



# 2015 SARE reporting for Tissues and Cells

## 2014 data

**Serious Adverse Reactions and Events**

**DG SANTE (Health and Food Safety)**

**Unit B4 – Medical Products: quality, safety, innovation**

Meeting of the Competent Authorities for Human Tissues and Cells

9-10 June 2016



- **Launch:** 11 June 2015
- **Deadline:** 31 July 2015
- **Submissions:**
  - Submissions: 29 countries
  - No submission: 1 country
- **Preliminary analysis:** presented in December 2015
- **Final results:** in June 2016



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# Reporting countries

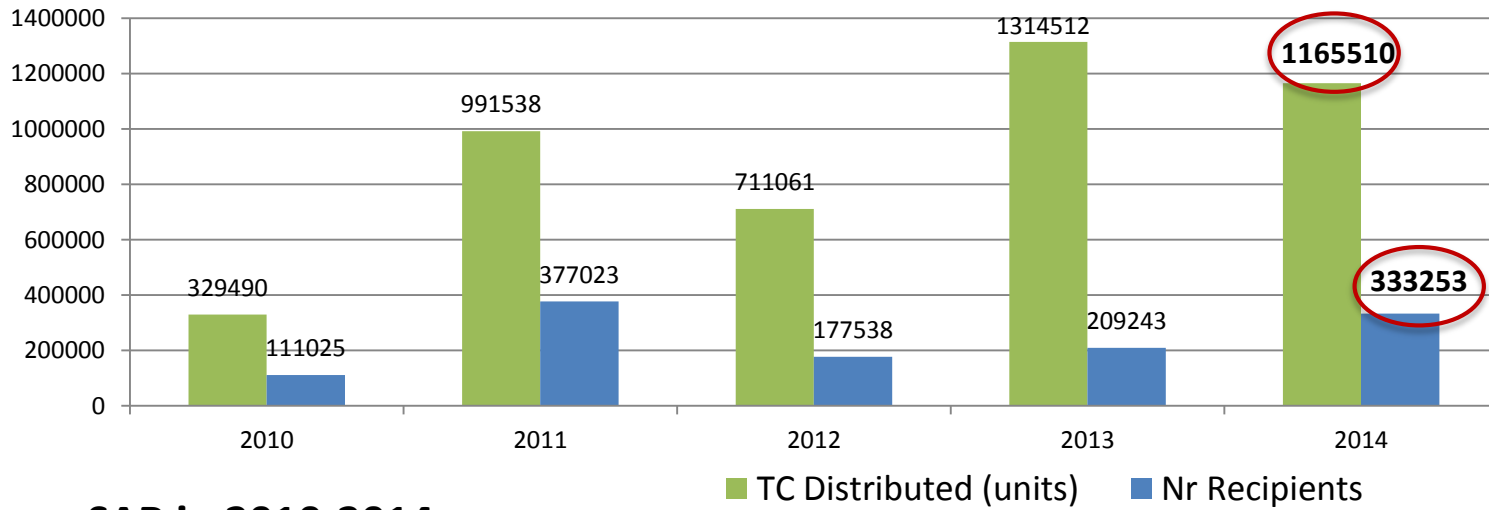
		<b>Denominators/ SAR/SAE</b>	<b>Non- reproductive</b>	<b>Reproductive</b>
Denominators for SAR	}	Number of TC distributed	24	15
		Number of recipients	15	11
		<b>SAR</b>	<b>12</b>	<b>10</b>
		SAR in donors	12	15
Denominator for SAE	}	Number of TC processed	16	
		<b>SAE</b>	<b>19</b>	

# SAR RESULTS 2010-2014

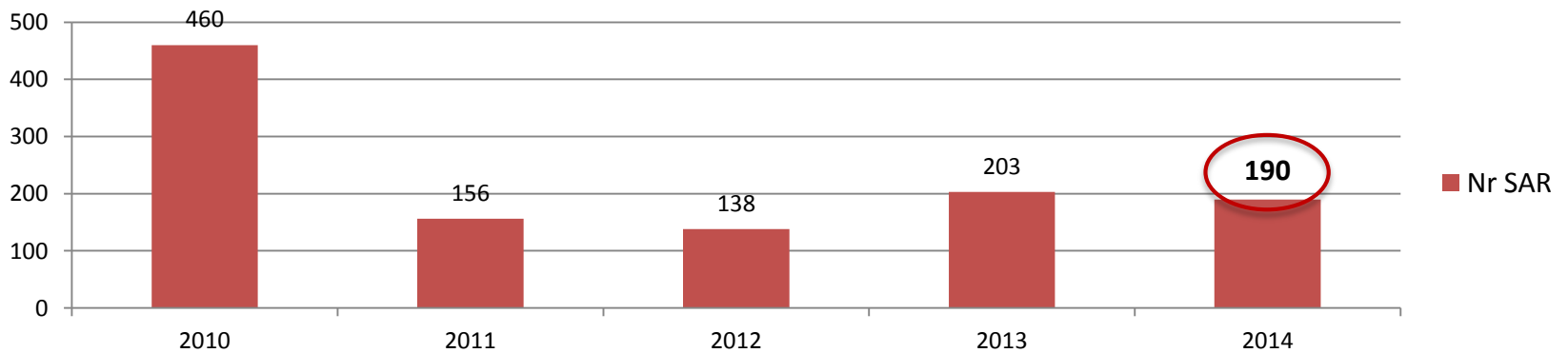


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## SAR Denominators 2010-2014



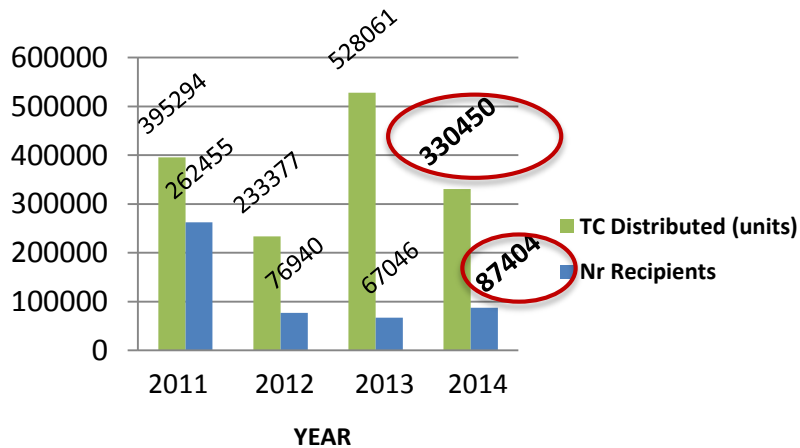
## SAR in 2010-2014



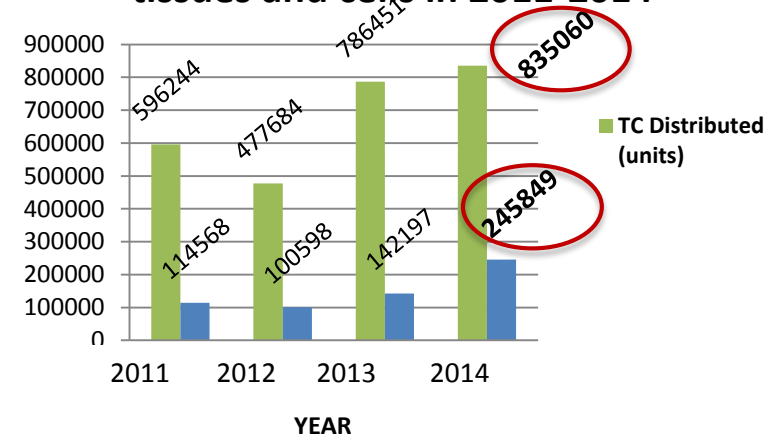


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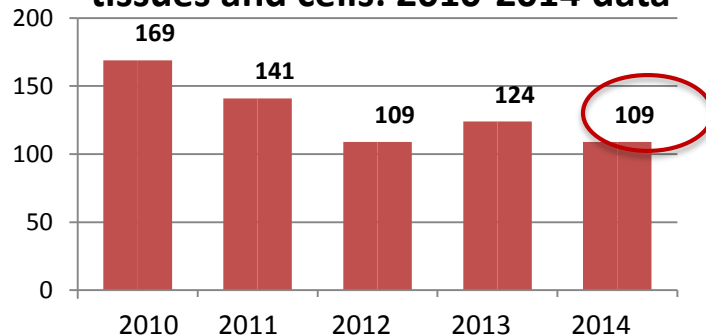
## Denominators for non-reproductive tissues and cells in 2011-2014



## Denominators for reproductive tissues and cells in 2011-2014

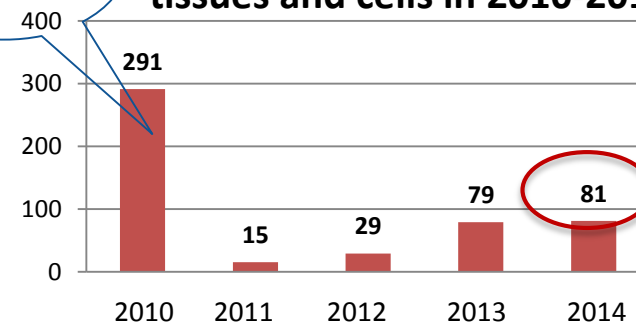


## Number of SAR for non-reproductive tissues and cells: 2010-2014 data



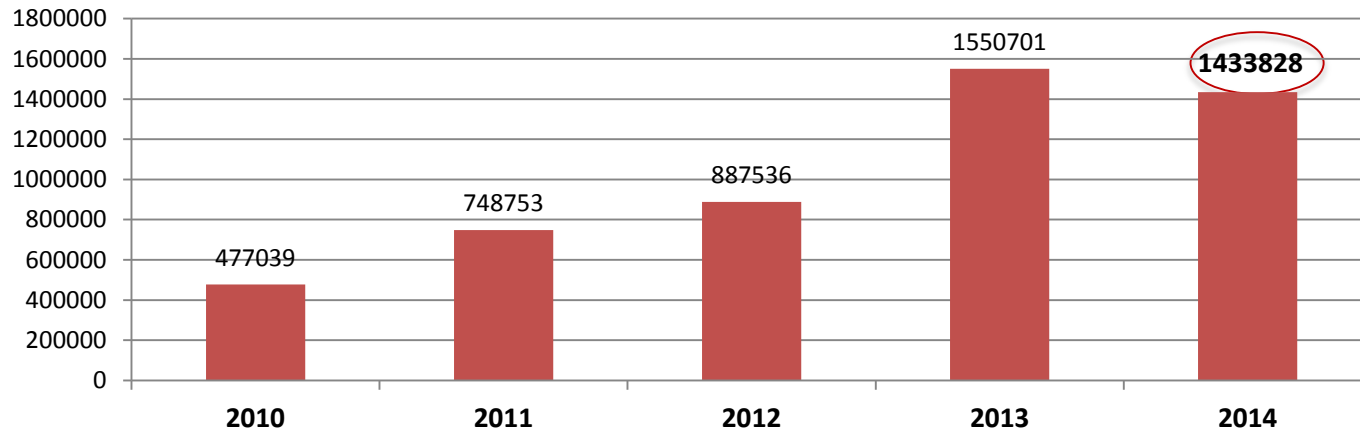
Including SAR  
in donors  
(OHSS)

## Number of SAR for reproductive tissues and cells in 2010-2014

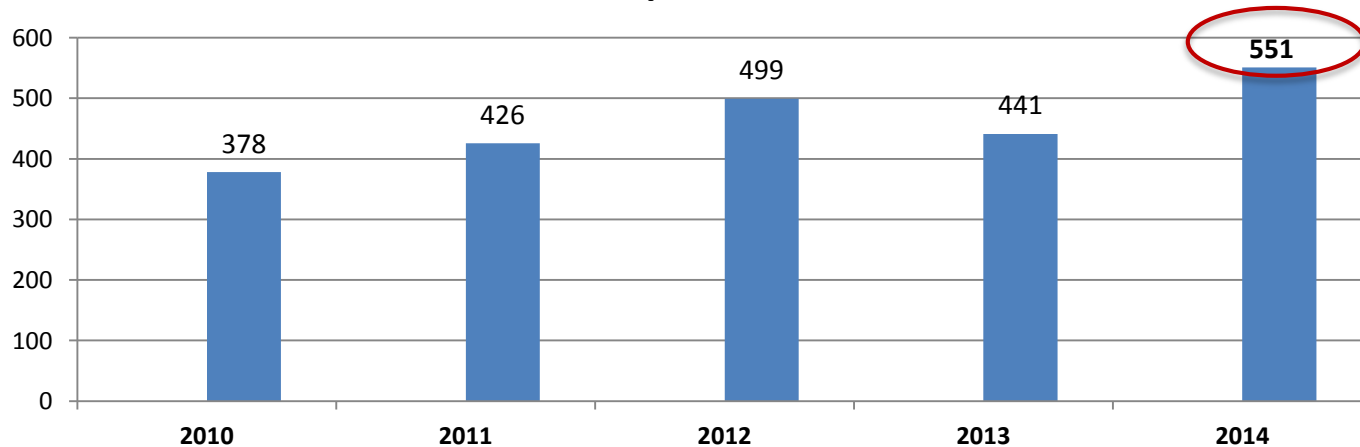




## Total nr of tissues and cells processed (units): 2010-2014 data



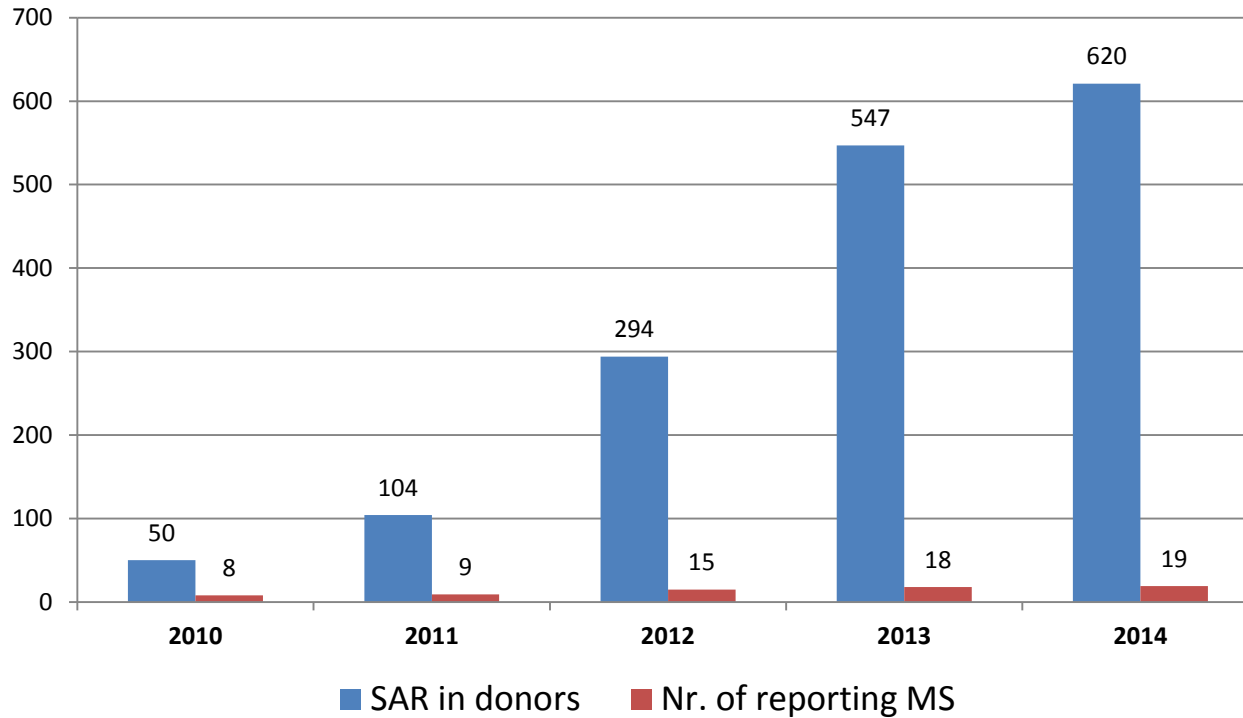
## Number of SAE reported: 2010-2014 data



# SAR in donors 2010-2014



## SAR in donors 2010-2014



**Voluntary  
Reporting!**

**2015  
Reporting countries:  
AT, BE, BG, CZ, DE, EE, ES,  
FI, FR, IE, IT, HR, NL, NO,  
PL, PT, SI, SE, UK**

# SAR RESULTS - 2014 -



- **Total SAR** reported: **190 SAR**
- - **Non-reproductive** tissues and cells
  - **109 SAR**
  - 12 countries (BE, DE, ES, FI, FR, IE, IT, NL, PT, SE, UK and NO)
  - 0,033% SAR/tissues and cells distributed TC distributed
  - 0,126 % SAR/number of recipients.
- - **Reproductive** tissues and cells.
  - **81 SAR**
  - 10 countries (BE, CZ, DK, ES, FI, IE, NL, SE, UK and NO)
  - 0,010% SAR/tissues and cells distributed
  - 0.033% SAR/number of recipients

Cautious  
interpretation

**14 countries → no SAR reported for 2014**

(AT, BG, CY, EE, EL, HU, HR, LT, LV, MT, PL, RO, SI and LI)

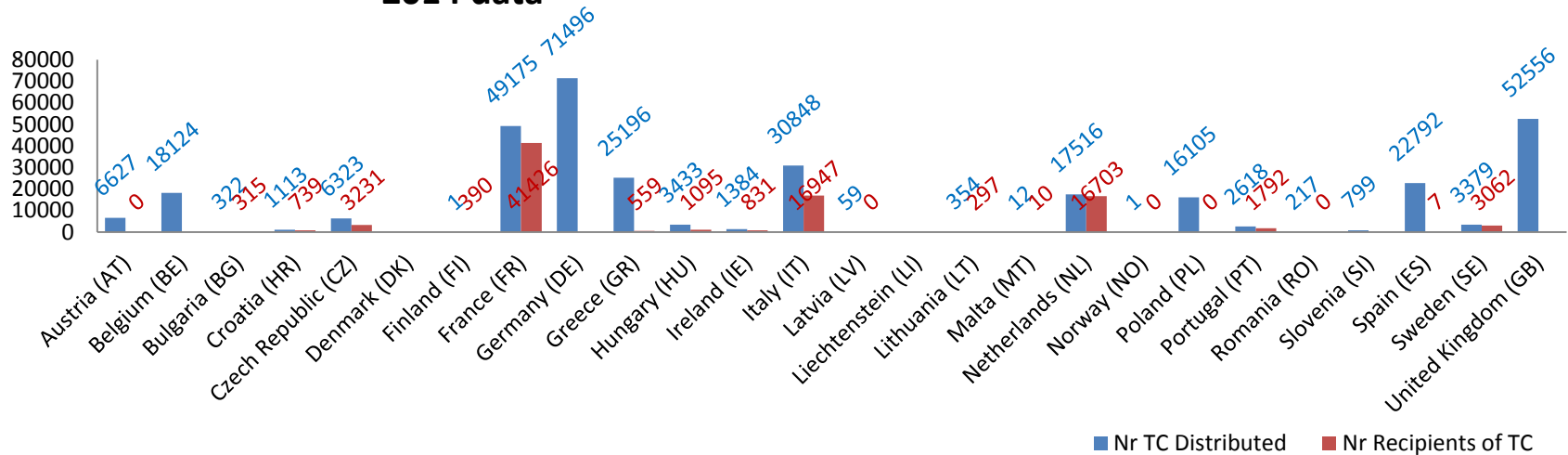


# SAR RESULTS - 2014 -

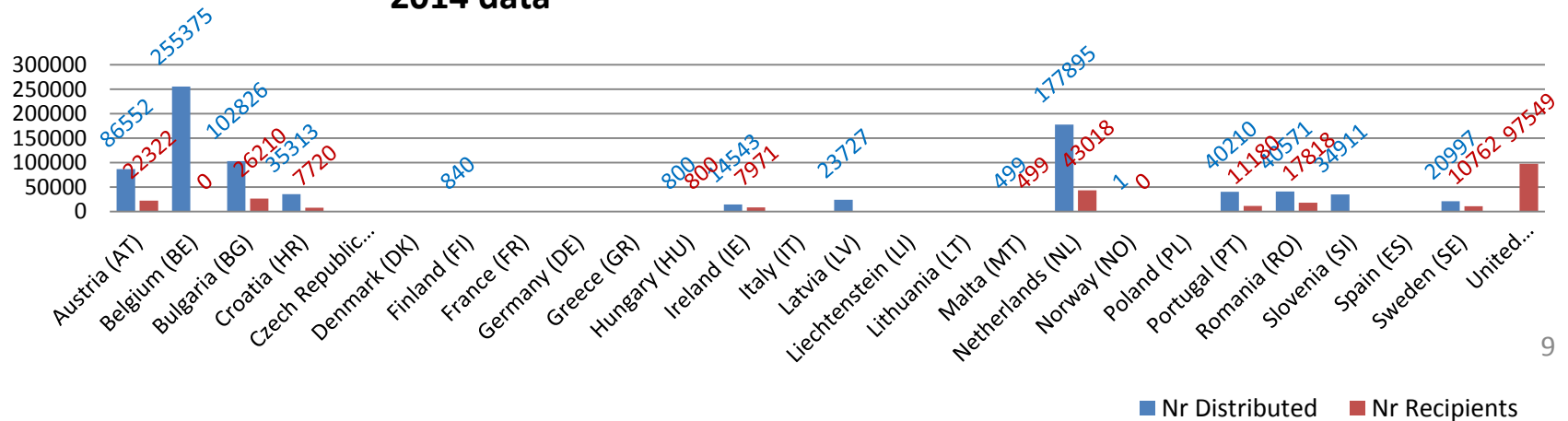


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## SAR denominators - Non-reproductive tissue and cells 2014 data



## SAR denominators – Reproductive tissues and cells 2014 data

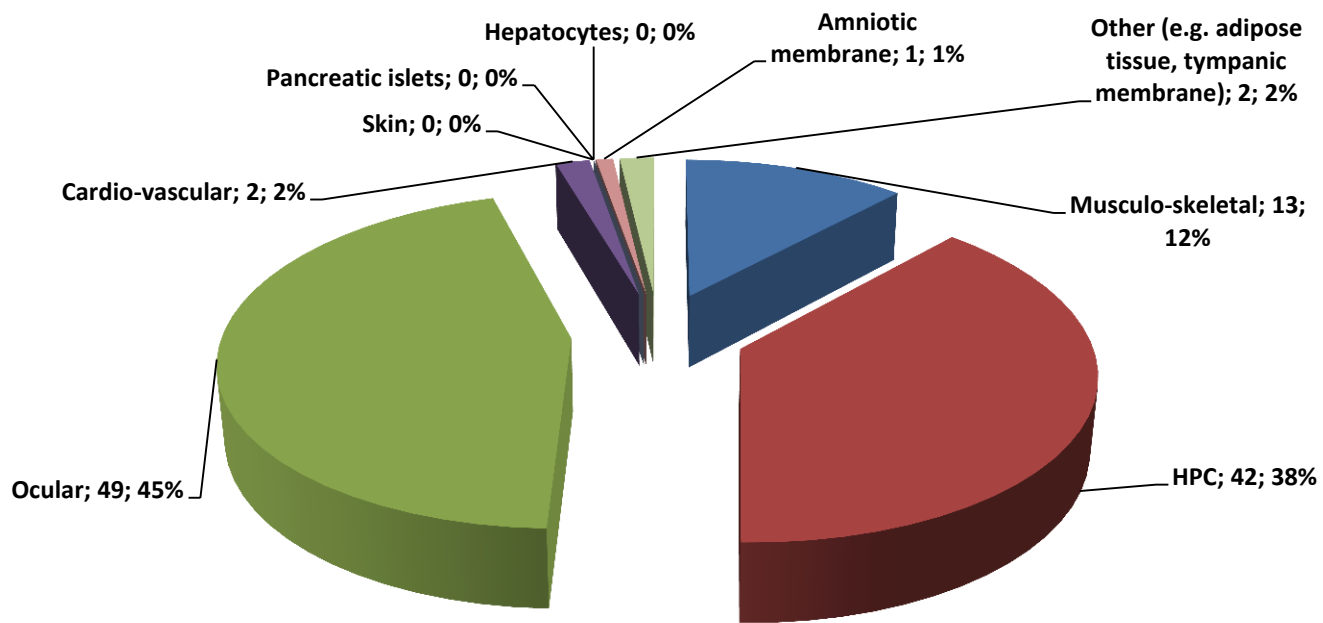




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### SAR/type of tissues and cells

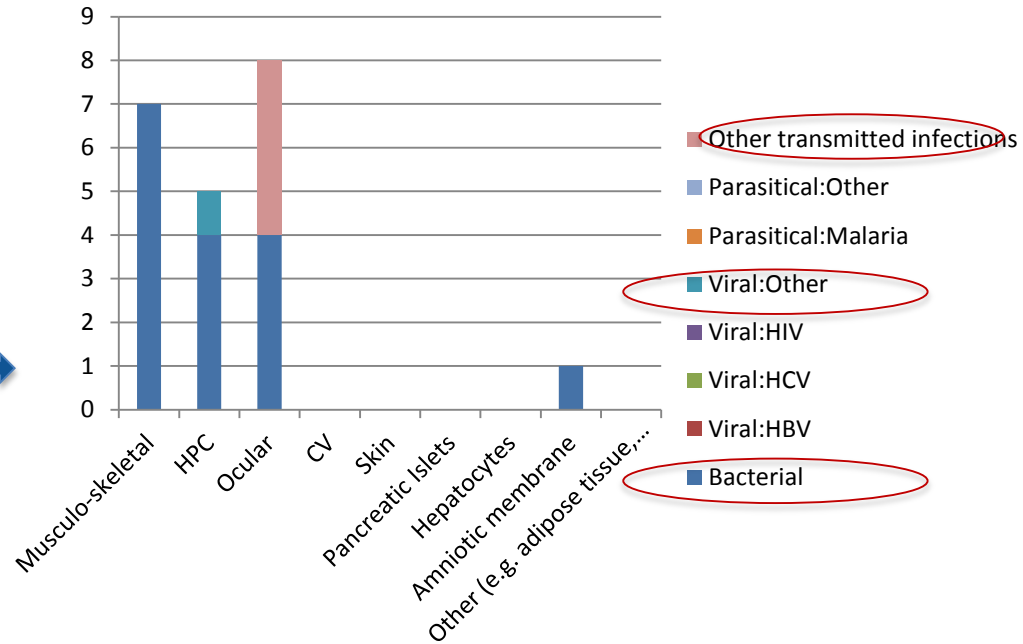
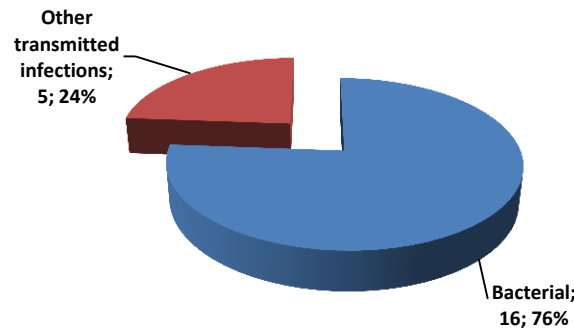
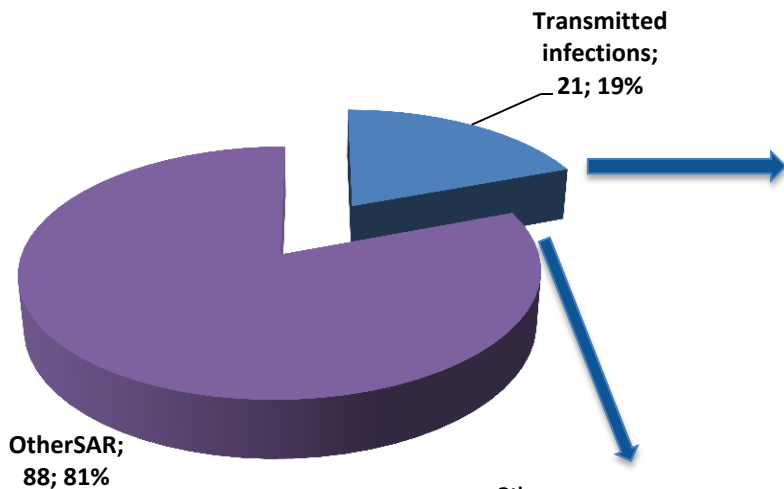
**Total SAR = 109**





### SAR specification

**Total SAR= 109**





### Musculo-skeletal tissues

**SAR = 13**

#### Transmitted infections = 7

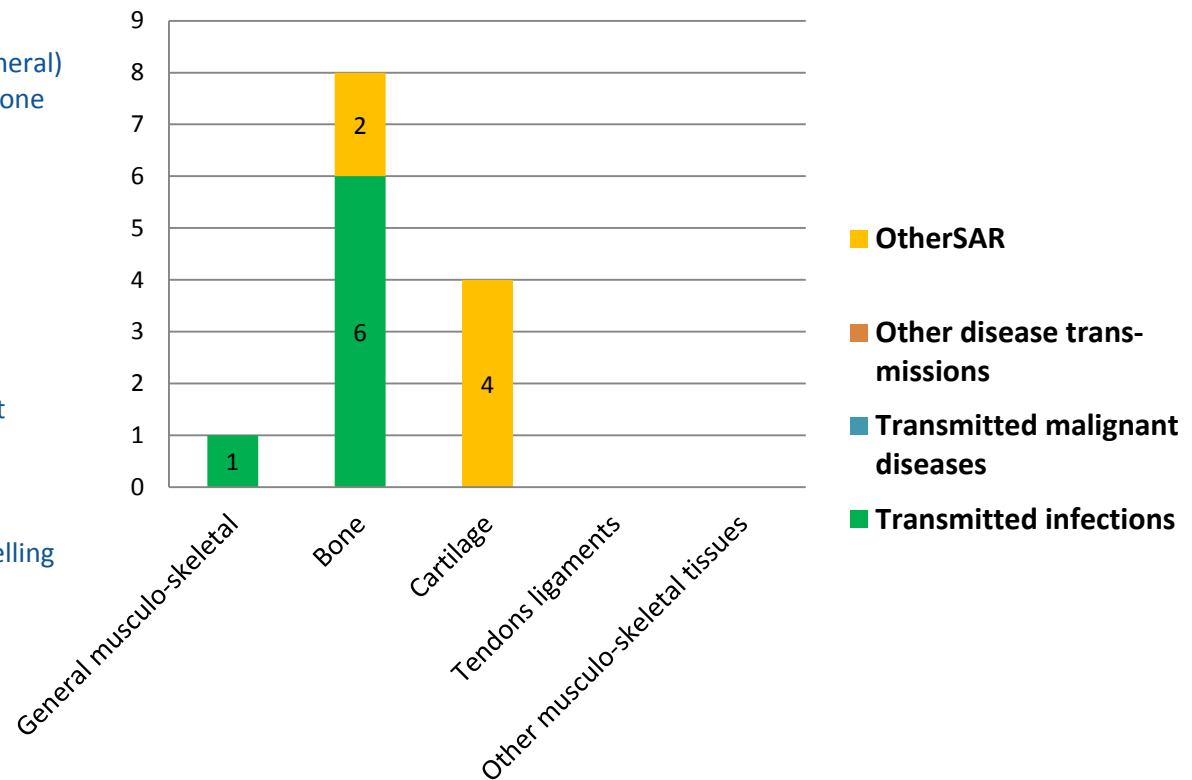
##### 7 bacterial infections

- 1 Bacterial infection in the graft implanted (general)
- 1 Possible growth of white Staphylococcus in bone sample
- 2 unknown
- 1 E.Coli, E.Coli ESBL and Enterobacter cloacae
- 2 Proprionibacterium Acnes

#### OTHER SAR = 6

- Bone (2)  
2dehiscences transplantation sites, lack of effect (bone)
- Cartilage (4):
  - Deep vein thrombosis
  - Influenza like illness, joint infection, joint swelling
  - Transplant hypertrophy
  - Bone edema, partial delamination

SAR musculo-skeletal tissues - 2014 data





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HPC

SAR = 42

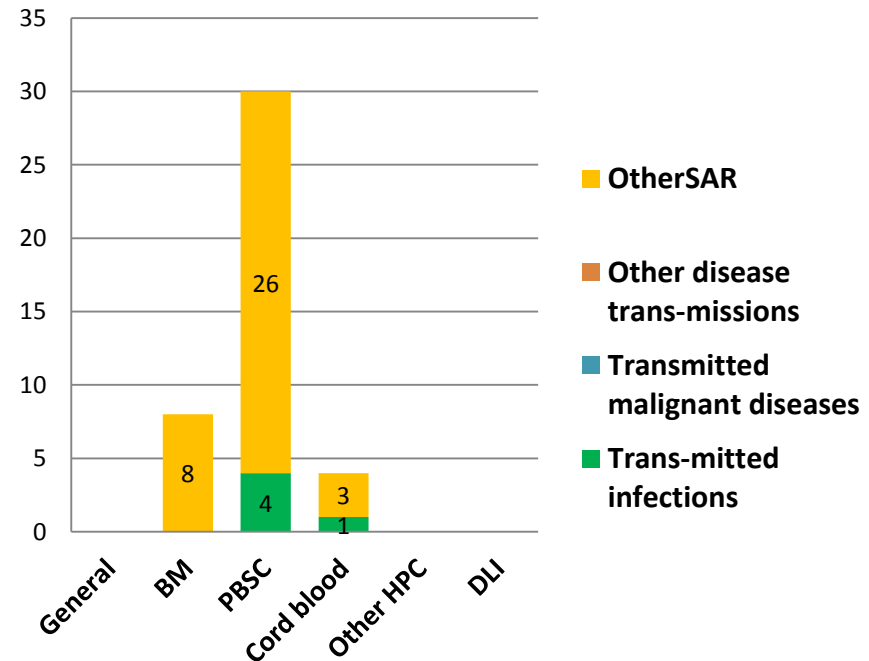
### Transmitted infections =5

- 4 bacterial infections
  - 1 Staphylococcus sepsis (PBSC)
  - 2 Fever after HPCs infusion (PBSC)
  - 1 Clinical decision made to infuse E.coli positive autologous CB resulted in infection in recipient (CB)
- 1 viral infection (other)
  - HHV6 (PBSC)

### Other SAR = 37

- Allergic: 4(PBSC)
- CV: 3 (BM), 4(PBSC)
- Pulmonary: 1 (BM), 2(PBSC)
- Renal: 0
- Neurological: 5(PBSC)
- Toxicity: 1(CB), 4(PBSC)
- None of the above: 13
  - Graft failure: 2 (BM), 1(CB), 4(PBSC)
  - 1 acute hemolytic crisis during the infusion of donor HSCs (BM)
  - 1 Acute renal tubular necrosis / hypertensive crisis / transient ischemic heart disease after autologous BM infusion
  - 1 Transplant recipient undergoing double red cell depleted cord transplant developed acute kidney injury; may be due to lysed red cells in cord blood
  - 2 fever (PBSC)
  - 1 loss of consciousness, admission to intensive care with intubation patient after autologous HPCs infusion (PBSC)

### SAR HPC - 2014 data





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Ocular tissues

SAR = 49

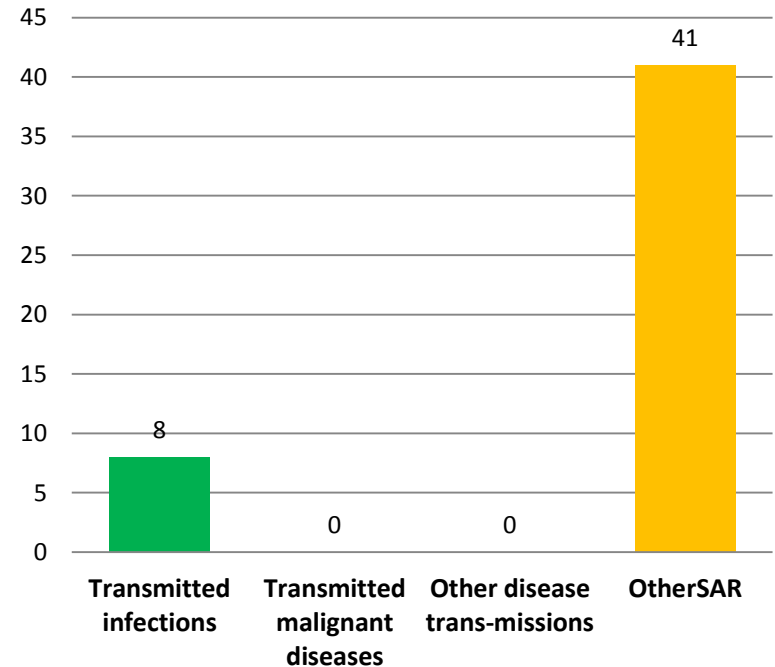
### Transmitted infections = 8

- 4 bacterial infections  
(e.g. 3 endophthalmitis; 1 defect in the functioning of the automated microbiological incubation/detecting system)
- 4 other transmitted infections
  - 1 Primary graft failure due to an infection- cornea released in accordance with eye bank's quality procedures, unable to confirm if the infection was transmitted from the donor or related to the quality of the cornea.
  - 1 Recipient developed endophthalmitis following corneal transplant. Two eyebanks were involved but so far, no clear evidence to implicate cornea as tests were negative.
  - 2 mycotic infections – confirmed

### Other SAR = 41

- 1 Leucoma
- 3 Graft failure
- 37 Graft rejection (1 country)

SAR Ocular tissue - 2014 data



### Cardio Vascular

**SAR = 3**

#### Other SARs

#### Heart valves (2)

#### Other SAR

- rupture of HV 2 weeks after transplant
- Pulmonary reaction: postoperative dilation of transplanted pulmonary valve; graft removed

### Amniotic membrane

**SAR = 1**

#### Transmitted infections (bacterial)

- ocular amniotic membrane infection

### Skin

### Pancreatic islets

### Hepatocytes

**SAR = 0**

# SAR 2014

## Reproductive T&C



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Country (Code)	Nr Distributed TC	Nr Recipients	Nr SAR
<b>GENERAL Sperm</b>	33396	20160	1
<b>Sperm - partner donation</b>	81025	84563	1
<b>Sperm - non partner donation</b>	30387	14382	42
<b>General oocyte</b>	148121	14586	3
<b>Oocyte - partner donation</b>	346737	60002	0
<b>Oocyte - non partner donation</b>	14042	4882	21
<b>Embryos</b>	180231	64484	12
<b>Ovarian tissue</b>	76	2	1
<b>Testicular tissue</b>	1045	40	0
<b>Other reproductive tissues</b>	0	0	0
	<b>835060</b>	<b>263101</b>	<b>81</b>

**SAR = 81**

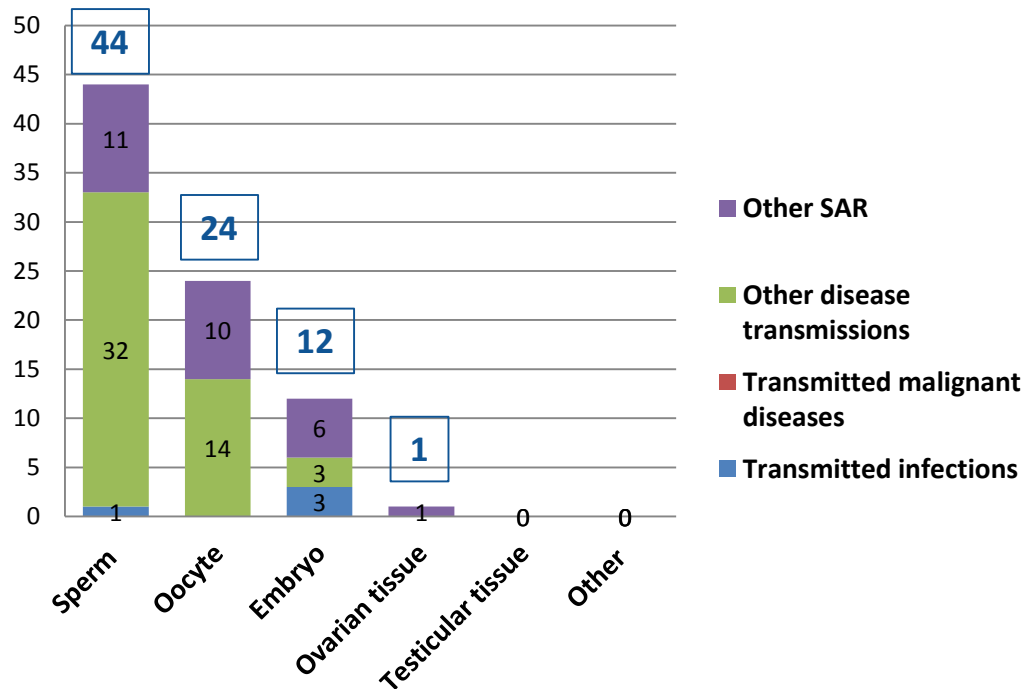
44

24





### SAR related to the application of gametes and embryos – 2014 data



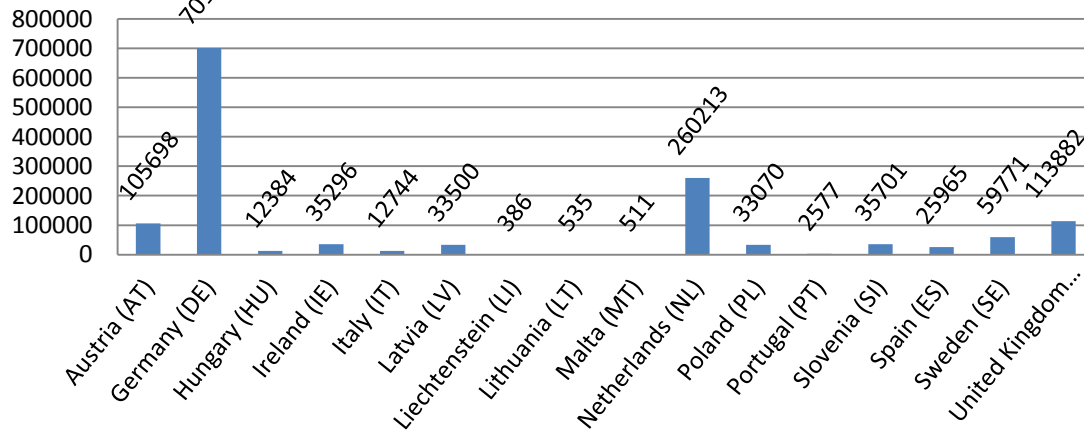
### SAR Reporting countries

- Sperm
  - General: CZ (1)
  - Partner: NL (1)
  - Non-partner: BE (12), DK (13), ES (14), IE (1), UK (2)
- Oocyte
  - General: CZ (3)
  - Non-partner: BE (2), ES (16), FI (1), UK (2)
- Embryos: CZ (1), ES (4), SE (6), UK (1)
- Ovarian tissue: NO (1)



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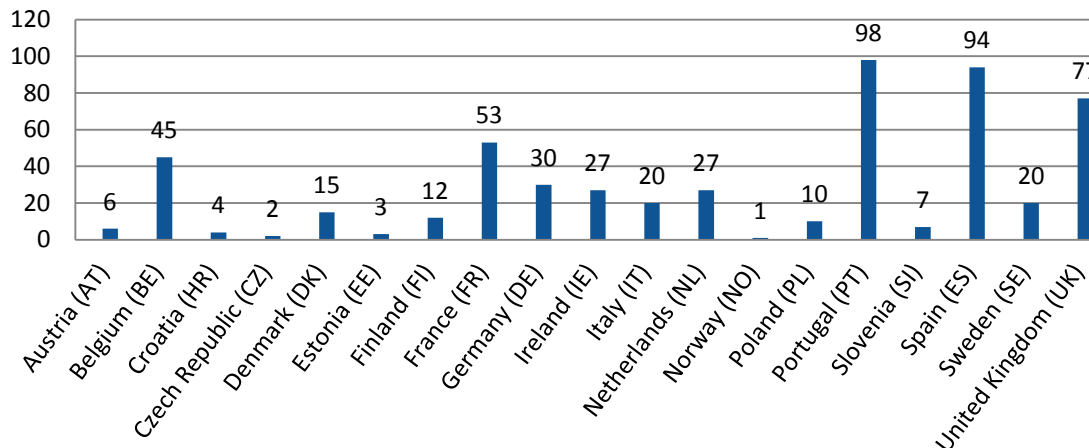
## Number of tissues and cells processed - 2014 data



**TC processed (units)  
= 1433828**

16 reporting  
countries

## SAE reporting/MS - 2014 data

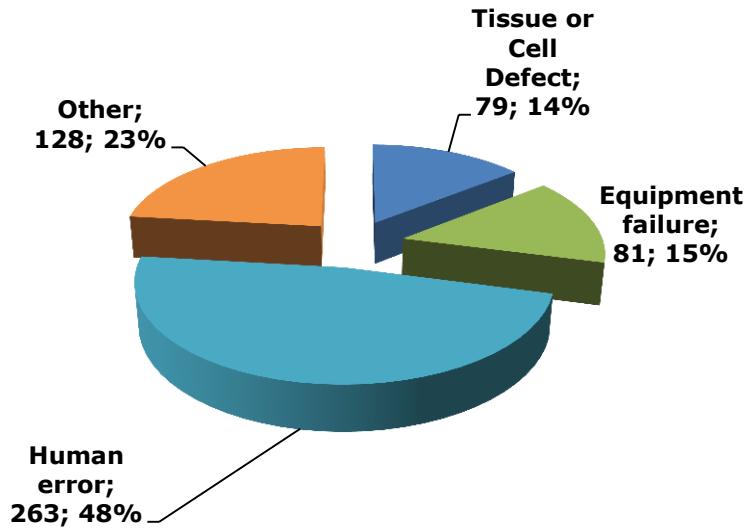


**Total SAE  
= 551**

19 reporting  
countries

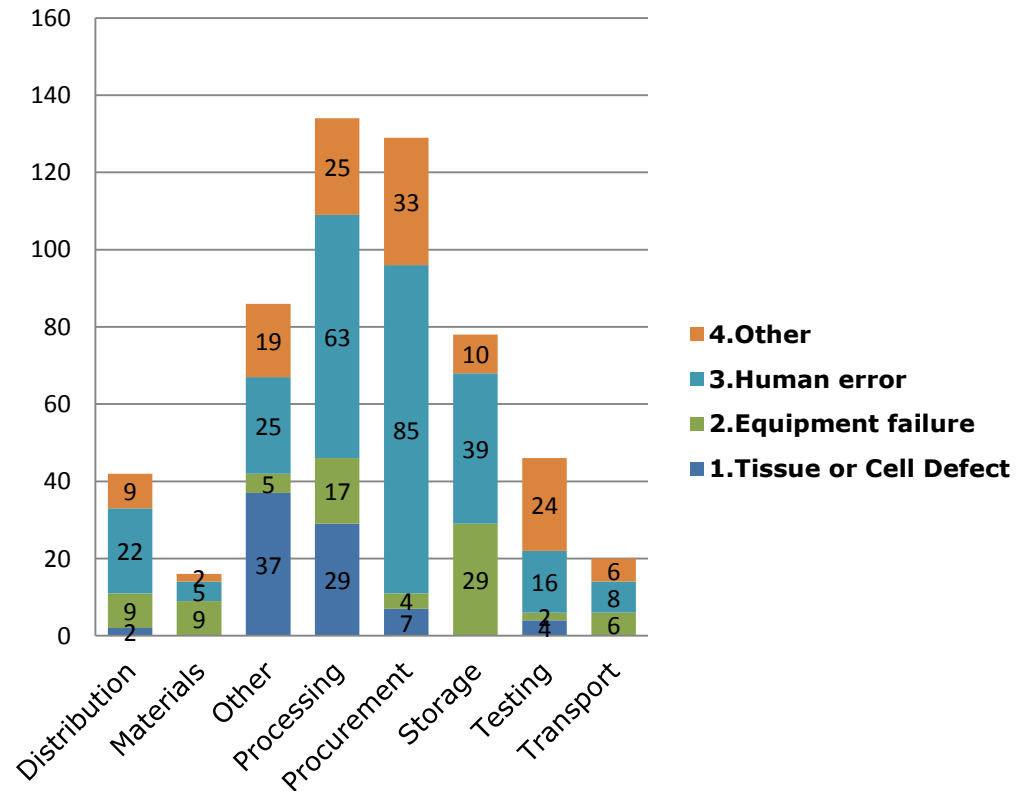


## SAE/category - 2014 data



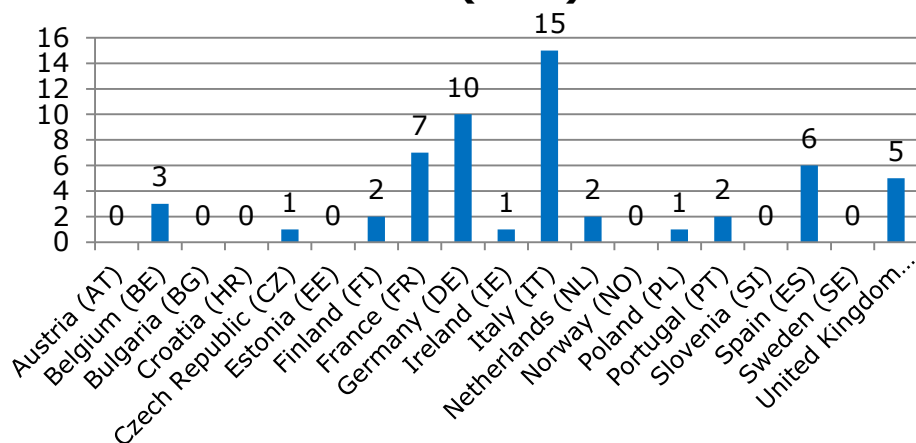
**Total SAE = 551**

## SAE specification/activity - 2014 data





## SAR in donors: Non-reproductive cells (HPC)

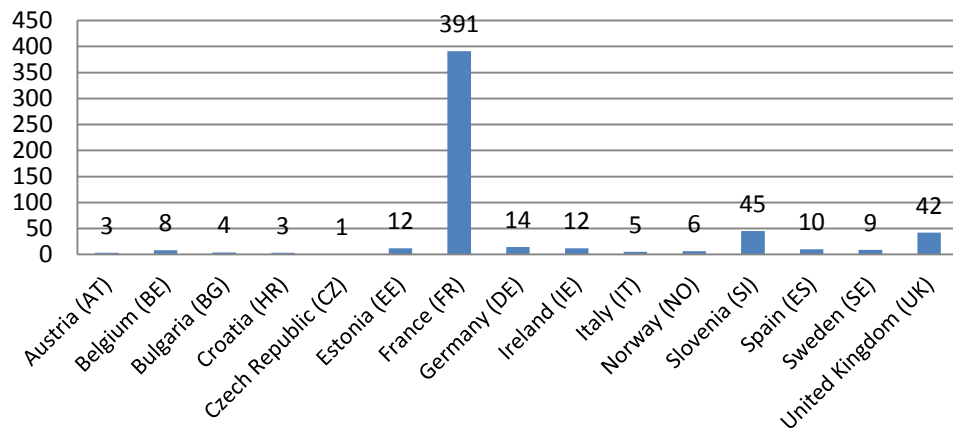


**SAR in donors = 620**

**Non-reproductive TC/HPC = 55**

- HPC: 53
- Cartilage 2

## SAR in donors: Reproductive cells



**Reproductive cells = 565**

- Oocytes general: 76 (43 OHSS)
- Oocytes non-partner: 7 (3 OHSS) donation
- Oocytes partner: 480 (326 OHSS) donation
- Other: 2 (ectopic pregnancies)

*372 cases of OHSS*



## **2015 SARE reporting exercise**

- Gradual improvement of data collection
- A number of countries do not report SAR and SAE
- Increasing number countries reporting SAR in donors
- Next steps:
  - Comments on the draft report from Competent Authorities – 30 July 2016
  - Revision of the draft report and publication – in the coming months



## **2016 SARE reporting exercise**

- Launching of exercise - June 2016
- Changes in the reporting template
  - SAE to be reported separately for non-reproductive and reproductive tissues and cells
  - New clarifications on SAE in the Common Approach
- Data from Competent Authorities – 2 months for submissions
- Presentation of preliminary analysis – next Competent Authority meeting



## Support from JA VISTART (WP4) – discussion points

- **Denominators in ART:** conderatation to change the units to cycles? VISTART to look at the feasibility and potential impact
- Collaboration with World Marrow Donors registry (**SEAR/SPEAR**)? To see if they have notifications for HPC from countries in absence from data from CA?
- Engage with **Eurocet**? To see if their data can be used (when needed)?
- **Indication on deaths** – should it be explored?
- Classification of **SAR by imputability** (as for blood): should it be introduced?
- Donor reactions: should we categorise them better?



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# Thank you!







## Transmitted bacterial infections

Annual reporting exercise	Total number of tissues and cells distributed	Total number of recipients	Total number of SAR	Total transmitted infections	Transmitted bacterial infections							
					Nr	Per type of tissue/cell						
						HPC	Musculo-skeletal	Ocular	Skin	Gametes	Other (amniotic membrane)	
2009	6178	2279	8									
2010	118538	63579	51	14	11	2	0	0	0	9	0	
2011	329575	111025	460	42	38	4	2	6	0	25	1	
2012	991538	377023	156	27	22	10	8	3	0	0	1	
2013	711067	177538	138	22	16	5	5	5	0	1	0	
2014	1314215	209243	203	33	27	9	13	3	2	0	0	
2015	1165510	333253	190	22	16	4	7	4	0	4	0	
<b>TOTAL</b>			<b>1207</b>	<b>160</b>	<b>130</b>	34	35	21	2	39	3	



## Transmitted viral infections

Annual SARE reporting exercise	Viral transmissions	
	Nr	Details
<b>2009</b>	0	NA
<b>2010</b>	0	NA
<b>2011</b>	3	1 CMV transmission (sperm); 1 HSV transmission (cornea); 1 HCV transmission (DLI)
<b>2012</b>	2	1 HEV transmission (DLI); 1 HHV6 transmission (PBSC)
<b>2013</b>	2	1 viral encephalitis (BM); 1 HHV6 (CB)
<b>2014</b>	1	1 Herpes simplex (PBSC)
<b>2015</b>	1	1 HHV6 (PBSC)
TOTAL	9	



Reproductive cells	Nr SAR	Details
<b>GENERAL Sperm</b>	1	Other SAR: incorrect information concerning Rh factor of donor
<b>Sperm - partner donation</b>	1	Bacterial infection - Salpingitis after IUI
<b>Sperm - non partner donation</b>	42	<p>32 Other disease transmissions</p> <ul style="list-style-type: none"> <li>1 Macrocrania, mental retardation</li> <li>1 Cryptorchidia</li> <li>1 Oculocutaneous albinism</li> <li>2 Brachial fistula and microtia</li> <li>1 Oesophagial atresia</li> <li>2 Unilateral renal agenesis</li> <li>1 Club foot</li> <li>2 Hypospadias</li> <li>1 Diabetes mellitus</li> <li>1 Edwards Syndrome (IVG week 16)</li> <li>1 Triple X Syndrome</li> <li>1 Pierre Robin Syndrome</li> <li>1 Muenke Syndrome</li> <li>1 SMA Type 1</li> <li>1 Dilated Cardio Myopathy</li> <li>1 possible but unconfirmed link</li> <li>13 number of sperm donors reported to agency for which SARs in an unknown number of recipients have been validated.</li> </ul> <p>10 Other SAR</p> <ul style="list-style-type: none"> <li>1 Malformation with nuchal cyst. IA, 40 year old woman</li> <li>1 Baby with vestigial tail (donor ovocytes too)</li> <li>1 Baby with congenital heart disease of Fallot (donor ovocytes too)</li> <li>1 Child with hemolytic anemia (donor ovocytes too)</li> <li>1 Baby with hip dysplasia (donor ovocytes too)</li> <li>1 Neuronal migration disorders (cyst blake bag) (donor ovocytes too)</li> <li>1 Dysplasia renal</li> <li>1 Septo-optic dysplasia</li> <li>1 Microdeletion terminal chromosome 2</li> <li>1 Fetal polymorphism</li> </ul>



Reproductive cells	Nr SAR	Details
<b>General oocyte</b>	3	3 Other disease transmissions: Norrie disease; Phenylketonuria; Chromosomal aberation de novo
<b>Oocyte - partner donation</b>	0	-
<b>Oocyte - non partner donation</b>	21	<p>11 Other disease transmissions</p> <ul style="list-style-type: none"> <li>• Aorta hypoplasia</li> <li>• Double excretory system and double megaureter</li> <li>• Metabolic Disease- phenylketonuria. Discovered in a ovocytes donor after she donated.</li> <li>• Newborn live with cystic fibrosis.</li> <li>• Polycystic kidney disease (week 34 of gestation)</li> <li>• Malformation incompatible with life (IVG). Potter syndrome suspected.</li> <li>• Congenital adrenal hyperplasia</li> <li>• Turner Syndrome</li> <li>• Baby born from egg donation affected by Trisomy 18</li> <li>• A child with trisomy 21</li> <li>• Child born as a result of egg donation has 2 genetic abnormalities following array CGH testing. i 2q37 terminal deletion developmental disorder and boney changes resembling Albright's Osteodystrophy, ii 15q11 duplication. These abnormalities – not inherited from the father.</li> </ul> <p>10 Other SAR</p> <ul style="list-style-type: none"> <li>1 Twins, boy born with microophthalmia (right eye), healthy girl.</li> <li>1 Girl born with suspected diagnosis of Coloboma. No clear genetic origin.</li> <li>1 Stillbirth at 28 weeks</li> <li>3 Multiple malformations incompatible with life</li> <li>1 Autism</li> <li>1 Trisomy 8 (IVG)</li> <li>1 Club foot</li> <li>1 Neural tube defects (IVG)</li> </ul>
	<b>24</b>	



Reproductive cells	Nr SAR	Details
<b>Embryos</b>	12	3 Transmitted infections (bacterial): not specified 3 Other diseases transmitted 1 Severe heart malformation (IVG) 1 thanatophoric dysplasia 1 pt underwent IVF PGD for a chromosomal translocation - scan revealed that pt carrying MCDA twins. CVS showed unbalanced translocation. Pt underwent termination 6 Other SAR: 2 thrombosis v cava after ET, 1 acute surgery (due to endometriosis) after ET 1 Anatomical malformations 1 Biliary atresia 1 Schiss association
<b>Ovarian tissue</b>	1	1 Other SAR: 1 OHSS
<b>Testicular tissue</b>	0	
<b>Other reproductive tissues</b>	0	

# Annex 4a RESULTS

## SAR in donors 2014

### SAR in donors of non-reproductive tissues and cells = 55

- HPC: 53
- Cartilage 2

Country (Code)	Total	Quantity	Description
Belgium (BE)	1	1	Spleen rupture: complication of Neupogen medication
Czech Republic (CZ)		1	fever, laboratory markers of inflammatory
Ireland (IE)		1	Allergic reaction to granulocyte colony-stimulating factor administered prior to procurement
Poland (PL)		1	Abnormal circulatory reaction in donor on induction into anesthesia for HSC procurement
Finland (FI)	2	1	Allergic reaction during donation (autologous HSC)
Finland (FI)		1	Serious bleeding after donation (catheter problem, autologous HSC)
Netherlands (NL)		1	Donor developed polyarthritis reumatica, 4 years after donation
Netherlands (NL)		1	Donor suffered from headache and vomiting during PBSC mobilisation with GCSF
Portugal (PT)		2	Inadequate procurement procedure (human error)
United Kingdom (GB)	5	1	Cardiac event in an anxious patient at time of attempted stem cell collection.
United Kingdom (GB)		2	Donor fainted after donating stem cells.
United Kingdom (GB)		1	Donor reaction could be due to citrate toxicity; however donor has a history of palpitations.
United Kingdom (GB)		1	Donor reaction possibly to medications used to prime donor for stem cell collection by apheresis.
Spain (ES)	6	1	Cardiovascular disorders secondary to apheresis
Spain (ES)		2	haemorrhage secondary CBU extraction and apheresis
Spain (ES)		1	Hypocalcemia secondary to apheresis
Spain (ES)		2	Infective reactions during the apheresis process.
France (FR)	7	1	acute hypocalcemia
France (FR)		2	acute urinary retention
France (FR)		1	heavy bleeding inducing sample's stop
France (FR)		1	hemifacial spasm
France (FR)		1	migraine
France (FR)		1	pain
Germany (DE)	11	2	allergic reaction
Germany (DE)		1	cerebral seizure
Germany (DE)		1	citrate reaction
Germany (DE)		1	headache, common cold symptoms, swelling face
Germany (DE)		2	minimal change glomerulopathy
Germany (DE)		1	spontaneous ankle joint effusion
Germany (DE)		1	supraventricular tachycardia, heart rate 200/min
Germany (DE)		1	vaginal, buccal and palatal aphthae
Italy (IT)	15	1	Cardiovascular reaction
Italy (IT)		1	Chills
Italy (IT)		1	Cholecystitis acalculous after the second allogeneic HPCs collection
Italy (IT)		1	Exertional angina and ischemic heart failure post allogeneic peripheral HPcs
Italy (IT)		1	Left side hemiparesis
Italy (IT)		1	Occurrence of ventricular extrasystoles, hypertension and hypokalemia during allogeneic peripheral blood collection
Italy (IT)		5	Paresthesia and tingling
Italy (IT)		3	Tetany from citrate
Italy (IT)		1	Tetany from EDTA

Country (Code)	Total	Quantity	Description
Belgium (BE)	2	1	Cartilage: deep venous thrombosis following cartilage biopsy procurement
Belgium (BE)		1	Cartilage: hemarthrosis following cartilage biopsy procurement

## SAR in donors of reproductive cells = 565



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# Annex 4b RESULTS SAR in donors 2014

### Oocytes general Total: 76

Country (Code)	Total	Quantity	Description
Czech Republic (CZ)	1	1	OHSS
Spain (ES)		1	OHSS case (unknowed hospitalization)
Belgium (BE)	8	8	Ovarian hyperstimulation syndrome
Sweden (SE)	9	4	bleeding after OP
Sweden (SE)		1	infection avter OP
Sweden (SE)		3	OHSS with ascites and hospital care
Sweden (SE)		1	ovarial torsion
Estonia (EE)	12	12	severe ovarian hyperstimulation syndrome cases
Slovenia (SI)	45	1	hematuria
Slovenia (SI)		11	intraabdominal bleeding
Slovenia (SI)		30	OHSS
Slovenia (SI)		3	trasmitted infection, ovarium inflammation

### Oocytes - non partner donation Total: 7

Country (Code)	Total	Quantity	Description
United Kingdom (GB)	1	1	Severe OHSS
France (FR)	2	1	Hémopéritoneum
France (FR)		1	OHSS
Spain (ES)	4	1	Ectopic gestation
Spain (ES)		2	Haemoperitoneum
Spain (ES)		1	OHSS case (requires hospitalization)

### Oocytes - partner donation Total: 480

Country (Code)	Total	Quantity	Description
Croatia (HR)	1	1	OHSS
Austria (AT)	3	3	serious OHSS
Bulgaria (BG)	4	1	Complications after collection oocytes by ovarian follicular puncture. Severity assessment - Fatal
Bulgaria (BG)		3	Complications after collection oocytes by ovarian follicular puncture. Severity assessment - Serious
Italy (IT)	5	2	bleeding at pick up
Italy (IT)		2	OHSS
Italy (IT)		1	ovarian torsion at pick up
Spain (ES)		3	Haemoperitoneum
Spain (ES)		2	OHSS cases (require hospitalization)
Norway (NO)	6	1	Abdominal pain. Ovarian torsion
Norway (NO)		4	OHSS
Norway (NO)		1	Transvaginal aspiration abscess
Ireland (IE)	12	11	OHSS
Ireland (IE)		1	Tubo-ovarian abscess after oocyte collection. Laparoscopic Drainage
Germany (DE)	14	12	OHSS
Germany (DE)		1	secondary bleeding after follicular puncture
Germany (DE)		1	severe pain after egg collection
United Kingdom (GB)	41	41	Severe OHSS
France (FR)	389	24	Adnexal torsion
France (FR)		1	Death (heart attack the day before the oocyte retrieval)
France (FR)		20	Infectious complication (abcess, peritonitis,..)
France (FR)		250	OHSS
France (FR)		20	Others
France (FR)		67	Surgical or anesthetic complication (hemoperitoneum, pelvic pain,..)
France (FR)		7	Thrombosis