

# euromedicat

## PROJECT FINAL REPORT

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## Declaration by the scientific representative of the project coordinator

I, as scientific representative of the coordinator of this project and in line with the obligations as stated in Article II.2.3 of the Grant Agreement declare that:

- The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;
- The project
  - Has fully achieved its objectives and technical goals for the period.
  - Has achieved most of its objectives and technical goals for the period with relatively minor deviations.
  - Has failed to achieve critical objectives and/or is not at all on schedule.
- The public website is:
  - up to date
  - not up to date
- To my best knowledge, the financial statements which are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project (section 3.4) and if applicable with the certificate on financial statement.
- All beneficiaries, in particular non-profit public bodies, secondary and higher education establishments, research organisations and SMEs, have declared to have verified their legal status. Any changes have been reported under section 4 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name of scientific representative of the Coordinator: **PROFESSOR HELEN DOLK**

Date: ..29../ April / 2015

Signature of scientific representative of the Coordinator: .....

## Final publishable summary report

### 1. Executive summary

**The EUROmediCAT project aimed to build a system for reproductive safety evaluation, to enable the systematic and comprehensive identification of possible adverse effects in pregnancy of medication in humans at the earliest stage post marketing and to enable the monitoring and evaluation of safety measures taken in Europe.** EUROmediCAT arose in the context of the unique paucity of information available regarding medication safety in pregnancy, especially as pregnant women are not included in premarketing clinical trials.

In EUROmediCAT, **15 European (EUROCAT) congenital anomaly (CA) registries in 13 countries** and **7 healthcare databases including prescription information in 5 countries** were used and linked to generate powerful datasets for the assessment of teratogenicity (ability to cause CA). We used (i) a central database of >160,000 livebirths and stillbirths with CA and terminations of pregnancy for fetal anomaly, with over 36,000 ATC-coded medication exposures, from a population of 7.2 million births 1995-2012 ii) a cohort of 1,879 pre-gestational diabetic pregnancies 1998-2012 linked to CA registries iii) healthcare databases 2000 or 2004 to 2010, linked to CA registries. We performed case-(malformed) control studies and cohort studies regarding CA risk. We also analysed medication exposure of all women prior to and during the three trimesters of pregnancy.

**EUROmediCAT studies focused on four medication groups for chronic conditions**, where women and clinicians need evidence to balance risks and benefits of different treatment choices. **Antiepileptics** were prescribed much less during than prior to pregnancy, with between-country variation regarding the prescribing of new rather than older more teratogenic antiepileptics. A case- control study tested the newest signal of teratogenicity of topiramate, but exposure prevalence in Europe is still too low to provide sufficient evidence. **Antidiabetics** have been increasingly prescribed since 2004, both insulins and oral antidiabetics, with prescribing of insulin analogues overtaking human insulins. Literature review indicated little existing research but no evidence of teratogenicity of insulin analogues. Our large diabetic cohort study confirmed lack of increased risk of CA with analogue use compared to human insulin, reassuring for women with diabetes. **Antiasthmatics** had a complex pattern of prescription, due to the effects of pregnancy on both medication use and asthma severity. Literature review found 10 signals of specific CA associated with use of antiasthmatics. The case-control and cohort studies confirmed some signals, refuted others, and found a small excess risk of all major CA combined, but effects of medication and of underlying asthma are difficult to disentangle. The results showed the importance of managing asthma actively and avoiding the need for high dose treatment of exacerbations. **SSRI** prescribing dropped during pregnancy, increased over time from 2004, and was much higher in the UK. Literature review found 15 signals of specific CA associated with SSRI use, including congenital heart defects. The case-control and cohort studies confirmed some signals and refuted others, finding raised risk of severe congenital heart defects with SSRI as a class and individually, with evidence of dose-response effect, but small and non- significant increased risk of major CA combined. **Systematic signal detection** using a 50% False Detection Rate generated signals in **other medication groups**, including 7 consistent with previous literature (female sex hormones and antiretrovirals), and 8 others requiring confirmation in independent datasets.

Online surveys and focus groups explored an emerging medication safety concern - the availability of highly teratogenic drugs such as isotretinoin for internet purchase without a prescription and outside the Pregnancy Prevention Programme. These studies further showed the importance of investigating women's medication-related behaviour, and their use of the internet for information.

**EUROmediCAT has shown that it is possible to use existing databases and multidisciplinary collaboration to improve medication safety for pregnant women. A set of Recommendations are being disseminated to improve reproductive pharmacovigilance in future.**

## 2. Summary description of project context objectives

### 2.1 Summary description of the project context

#### Background

Teratogenicity - risk of congenital anomaly - is of major importance in decisions about medication (medicine/drug) safety in pregnancy. When medicines are licensed for marketing, information with respect to reproductive toxicity is only available from pre-marketing animal studies which are seriously limited in their ability to predict human teratogenesis. Pregnant women are excluded from pre-marketing clinical trials in humans, so the safety of medicines in pregnancy has not been established at the time that a medicine is licensed. Post-marketing surveillance of teratogenic effects in humans is essential. Most medicines are subject to special warnings because they have not been sufficiently studied during pregnancy to know the possible risks, even medicines which have been on the market for many years. Pregnant women with chronic or long term conditions such as diabetes, epilepsy, asthma and depression need treatment during pregnancy. Safety information about the drug classes relating to these diseases is a particular priority, so that the appropriate medication choices can be made. Furthermore, as many pregnancies in Europe are unplanned, some medicines may be taken unintentionally during organogenesis before the pregnancy has been recognised, and safety issues related to such use need evaluation. To address these issues, it is important to build a systematic post-marketing surveillance system to evaluate safety of drugs in pregnancy so better information can be provided to health care professionals and patients.

**To develop and test an efficient system for safety evaluation of drugs during pregnancy based on an existing network of congenital anomaly registers in Europe (EUROCAT) combined with existing healthcare databases.**

#### *The role of congenital anomaly registries in Europe*

In the post-marketing setting, three main approaches have been used in the last few decades, albeit not in a co-ordinated or systematic way, to identify teratogenic risks associated with medicine use in pregnancy: spontaneous adverse reaction reporting, cohort studies, and case-control studies. Spontaneous reporting is most useful for early detection of very high risks of a specific congenital anomaly, but is subject to high rates of false positive and false negative findings. Cohort studies, which include “pregnancy registry” studies of specific medicines set up by industry, cohorts of exposed women who contact Teratogen Information Services, and medical-condition based cohorts set up by consortia of clinical specialists, are most useful for early detection of high risks of congenital anomalies. Large study numbers are difficult to build up through individual notification and follow-up. Case-control studies based on congenital anomaly registries can achieve large study populations and thus study specific congenital anomaly risks and moderate risks, but had been under-exploited in Europe for their pharmacovigilance potential, a situation to be addressed therefore in the EUROmediCAT project.

Congenital anomaly registries, which have their early origins in the wake of the Thalidomide disaster with the aim of detecting a possible new teratogen at the earliest stage possible, are a crucial part of the post-marketing surveillance system. The EUROmediCAT project is built on an existing network of congenital anomaly registries, the European Surveillance of Congenital Anomalies (EUROCAT) network. Registries send individual anonymised records to a central database. Medication exposure information is mainly based on hospital medical files. The EUROmediCAT project enabled the enhancement, validation and description of

the quality of medication exposure information held in the central database and the testing of other distributed database models.

#### *Data linkage between congenital anomaly registries and prescription databases*

The EUROmediCAT project set out to test innovative approaches using congenital anomaly registries: a) to link registries to healthcare databases including prescription data, identifying the advantages and problems of linkage b) to perform case-malformed control studies using enhanced data c) to link registries to chronic condition pregnancy cohorts (using diabetes as an example) to combine the advantage of a cohort approach to collecting tailored exposure information with standardised and complete outcome assessment and an internal unexposed comparator group in registries d) to link CA registries to population healthcare databases including all births to perform population cohort studies.

#### *Systematic signal detection and evaluation*

As defined by the WHO, a signal is reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. In all studies conducted, the EUROmediCAT project adopted a rigorous approach using systematic literature review to establish signals to be tested/evaluated and exploratory analysis to detect/generate new signals. Signal detection as a systematic activity (as opposed to signals generated by specific studies) is a field of pharmacovigilance activity mainly conducted in the context of spontaneous adverse reaction reporting. A central and well recognised problem is multiple testing, resulting in many false positives or “statistical noise”. In EUROmediCAT we sought to develop a system of systematic signal detection using unbiased population-based data, and statistical approaches to the multiple testing problem based on specifying false detection rates.

#### **To quantify the risk of congenital anomaly related to four drug classes: antiepileptics, insulin analogues anti-asthmatics, and antidepressants (SSRIs)**

Many women with chronic conditions need to continue their medication during pregnancy as stopping medication can put both the pregnant woman and the fetus at serious risk of the underlying disease. The choice of which medication to take depends on the weighing of risks and benefits of each. However, there is insufficient safety data on the risk of congenital anomaly associated with their use in pregnancy to inform decision-making by women and clinicians. Unintended exposures can also occur as women may not be aware of their pregnancy in early pregnancy, a period uniquely vulnerable to teratogenic effects.

The pharmacoepidemiologic literature on the four selected drug classes prior to (and during) EUROmediCAT presented different problems for each:

*Antiepileptics:* The teratogenic effects of first generation antiepileptics, and in particular valproic acid (sodium valproate) are well recognised but evidence regarding the newer antiepileptics is scarce. EUROmediCAT therefore concentrated on testing signals in relation to newer antiepileptics, particularly topiramate, using the central database in which exposure information for antiepileptics is well validated.

*Antidiabetics (Insulin analogs):* Diabetes is well known to be teratogenic unless there is good glycaemic control. There is a long history of human insulin use, but in recent years, insulin analogs (synthetic insulins) have increasingly been used, including in pregnancy, but without extensive safety information for pregnancy. EUROmediCAT therefore concentrated on testing insulin analogues, in a study design (linkage

with diabetes cohort) that could capture sufficient information about the underlying diabetes and its control.

*Antiasthmatics:* Asthma and use of antiasthmatics is increasing in the general population, and is much more common than epilepsy or diabetes, but little is known about the safety of antiasthmatics, which are often used in combination, in pregnancy. EUROmediCAT therefore evaluated congenital anomaly risk related to the range of antiasthmatics and their combinations, using both the central database and the new linkage approaches.

*Antidepressants (SSRIs):* The most common antidepressants in use currently are SSRIs. Since 2005 there has been concern about a possible association with congenital heart defects, particularly in relation to one type of SSRI, paroxetine. EUROmediCAT set out therefore to evaluate this signal and other signals published since, using both the central EUROmediCAT database and new linkage approaches. Due to the very large study population size EUROmediCAT could investigate whether there is evidence for difference in risk between individual SSRIs, whether specific types of congenital heart defects are associated with exposure and whether other non-heart congenital anomalies are associated.

The approaches utilised harness the huge study population available to look at specific congenital anomalies, rather than combining congenital anomalies together, since most teratogens have specific effects.

### **To develop a framework for evaluation of the efficacy of pregnancy-related drug safety measures**

Providing better information on teratogenicity is one part of improving medication safety in pregnancy. Clinicians and women alter their decisions regarding medication choice in pregnancy as a result of safety information available, and it is important to monitor the resulting trends in the prevalence of medication use in pregnancy, using healthcare databases. In the EUROmediCAT project, we “twinned” drug (medicines) utilisation studies with risk studies for the four drug groups: antiepileptics, antidiabetics, antiasthmatics and antidepressants. When it comes to the prescribing of medicines to pregnant women, there is the potential for regional variation in the type and frequency of prescribing. This results from the fact that there are no European-wide guidelines, that there can be different interpretations of the scientific evidence, that the clinical indications for which certain products are prescribed can vary and that there is regional variation in the prevalence of specific medical conditions. An understanding of variations in medicine utilisation patterns can be helpful in providing information on the number of pregnant women and women of childbearing age using specific products, as well as informing the interpretation of potential safety signals and identifying areas requiring further attention, investment and research. The drug utilisation studies of EUROmediCAT aimed therefore to describe and quantify the use of medicines during pregnancy and during the year before and after pregnancy, in different regions of Europe, using data from electronic healthcare databases and to evaluate the extent to which this was in accordance with (inter) national recommendations for the four drug groups in interest.

For drugs which are known teratogens with such a high risk that pregnancy must be avoided, pregnancy prevention programs (PPPs) have been developed. The efficacy of existing PPPs needs to be evaluated together with the reasons for success or failure. However, there are no formal monitoring systems for PPPs and this is an area for development therefore looked at by EUROmediCAT.

The use of the internet by pregnant women in Europe is growing, and can provide both access to teratogenic drugs, and to safety information about drugs. The growing role of the internet needs evaluation

to develop appropriate medication safety measures. This requires quite different methodological approaches than the traditional pharmacepidemiological study designs – reviewing internet sites, and investigating women’s behaviour when purchasing medicines and seeking information.

## 2.2 Main objectives of EUROmediCAT

The central aim of EUROmediCAT is to build a European system for reproductive safety evaluation, which enables us to identify systematically and comprehensively the possible adverse effects in pregnancy of a drug in humans at the earliest stage post marketing, and enables us to monitor and evaluate safety measures undertaken in Europe. The specific scientific objectives of EUROmediCAT are:

- To develop and test an efficient system for safety evaluation of drugs during pregnancy, based on an existing network of congenital anomaly registers in Europe (EUROCAT) combined with existing healthcare databases.
  - To develop further the EUROCAT database for systematic case-malformed control surveillance identifying associations between specific drugs and specific malformations, for signal detection and evaluation (see Workpackage 2)
  - To develop and test linkage between registers and population-based prescription databases for signal detection and evaluation (see Workpackage 3)
  - To develop and test linkage between registers and cohorts of pregnant women with chronic diseases for signal detection and evaluation (see Workpackage 5).
  - To evaluate further healthcare and other databases across Europe for their potential utility for drug safety in pregnancy research (see Workpackage 2, 5, 6).
- To quantify the risk of congenital anomaly related to four drug classes:
  - New anti-epileptics (AEDs) (see Workpackage 4)
  - Insulin analogues (see Workpackage 4)
  - Anti-asthmatics (see Workpackage 5)
  - Selective serotonin-reuptake inhibitors (SSRIs) (see Workpackage 5).
- To develop a framework for evaluation of the efficacy of pregnancy-related drug safety measures including:
  - Drug utilisation studies (see Workpackage 6),
  - Monitoring of the effectiveness of pregnancy prevention programmes (see Workpackage 6 and 7),
  - A scoping study of the role of internet access by pregnant women to drugs, and to safety information (see Workpackage 7)

EUROmediCAT project paid special attention to dissemination activities and the compilation of Recommendations for regulatory agencies, public health authorities and other policy makers (see Workpackage 8).

### 3. Description of the main S&T results/foregrounds

#### 3.1 Introduction

The EUROmedICAT project was subdivided into eight work packages, two relating to coordination and management and six scientific work packages (**Figure 3.1**). The EUROmedICAT project generated scientific assets such as datasets (**Table 3.1**), protocols, scientific studies (**Table 3.2**) and dissemination output (**Chapter 5**). The EUROmedICAT project generated three datasets which were subsequently used for scientific research. These datasets will continue to be available for scientific research following the completion of EUROmedICAT. In addition to these datasets, data management and pharmacovigilance software was developed under WP2.

**Table 3.1:** Overview of datasets generated by EUROmedICAT

Dataset	Description
<b>Dataset A</b>	The pre-existing EUROCAT database was updated to capture ATC-coded medication exposure for cases born from 1995 under WP2. This became EUROmedICAT database A, the project's main database consisting of 166,016 congenital anomaly registrations covering a total population of 7.4 million births in 13 countries. This dataset was used for setting up a post marketing surveillance system under WP2, and for case-malformed cohort studies performed under WP4 and WP5.
<b>Dataset B</b>	WP3 is responsible for linkage of five prescription databases with pre-existing EUROCAT CA registries in four countries using software developed under WP2. The linked dataset would be maintained under WP2 (Dataset B).  These four linked datasets were originally intended to be combined into a single database. Due to data protection issues discussed later, a distributed database model was implemented. This database was used for the analysis of anti-asthmatics and SSRIs in relation to CA under WP5.
<b>Dataset C</b>	A diabetic cohort was created under WP2 and linked to CA registries in seven countries, to be used for the WP4 study on antidiabetics in relation to congenital anomalies.

**Table 3.2:** Original scientific research and literature review was performed by EUROmedICAT

Study type	Work package	Description
<b>Signal detection study</b>	2	A systematic signal detection study was performed using <b>dataset A</b> using the pharmacovigilance data summary software.
<b>Methodology description</b>	3	A paper on the methodology and results of the prescription data linkage was produced.
<b>Literature review</b>	4	Literature review investigating the relationship between AED use and CA.
<b>Literature review</b>	4	Literature review investigating the risk of specific CA for diabetic pregnancies exposed to insulin analogues compared to human insulin exposed pregnancies.
<b>Cohort study</b>	4	Cohort study utilising <b>dataset C</b> involving diabetic women investigating the relationship between insulin analogues and CA.
<b>Case-malformed control study</b>	4	Case-malformed control study utilising the EUROCAT AED drug database investigating the relationship between AED and CA.
<b>Survey</b>	5	Survey of the potential of birth cohort study databases for use in medication studies in collaboration with CHICOS.
<b>Case-malformed control study</b>	5	Case-malformed control study utilising <b>dataset A</b> investigating the relationship between anti-asthmatics and CA.
<b>Case-malformed</b>	5	Case-malformed control study utilising <b>dataset A and B</b> investigating the

<b>control study</b>		relationship between SSRIs and CA.
<b>Population linkage study</b>	5	Population cohort linkage study utilising <b>dataset B</b> investigating the relationship between anti-asthmatics and CA.
<b>Population linkage study</b>	5	Population cohort linkage study utilising <b>dataset B</b> investigating the relationship between SSRIs and CA.
<b>Data resource description</b>	6	Study describing eight electronic healthcare databases in Europe including the five involved in <b>dataset B</b> in terms of population covered, data sources and key variables required for evaluating medicine use in pregnancy.
<b>Drug utilisation study</b>	6	Drug utilisation study utilising seven prescription databases including all five involved in <b>dataset B</b> investigating drug utilisation of anti-asthmatics in pregnant women.
<b>Drug utilisation study</b>	6	Drug utilisation study utilising six prescription databases including four involved in <b>dataset B</b> investigating drug utilisation of SSRIs in pregnant women.
<b>Drug utilisation study</b>	6	Drug utilisation study utilising seven prescription databases including all five involved in <b>dataset B</b> investigating drug utilisation of antiepileptics in pregnant women.
<b>Drug utilisation study</b>	6	Drug utilisation study utilising seven prescription databases including all five involved in <b>dataset B</b> investigating drug utilisation of insulin analogues in pregnant women.
<b>Drug utilisation study / policy evaluation study</b>	6	Drug utilisation and policy evaluation study utilising five prescription databases involved in <b>dataset B</b> investigating drug utilisation of drugs targeted by pregnancy prevention programs due to teratogenicity in pregnant women.
<b>Descriptive cross-sectional survey</b>	7	Survey of 50 E-pharmacies in relation to adherence to pregnancy prevention programs for teratogenic drugs.
<b>Online survey and focus groups</b>	7	Online survey and online focus groups relating to use of internet for medication purchase and medication safety information

Workpackage overview

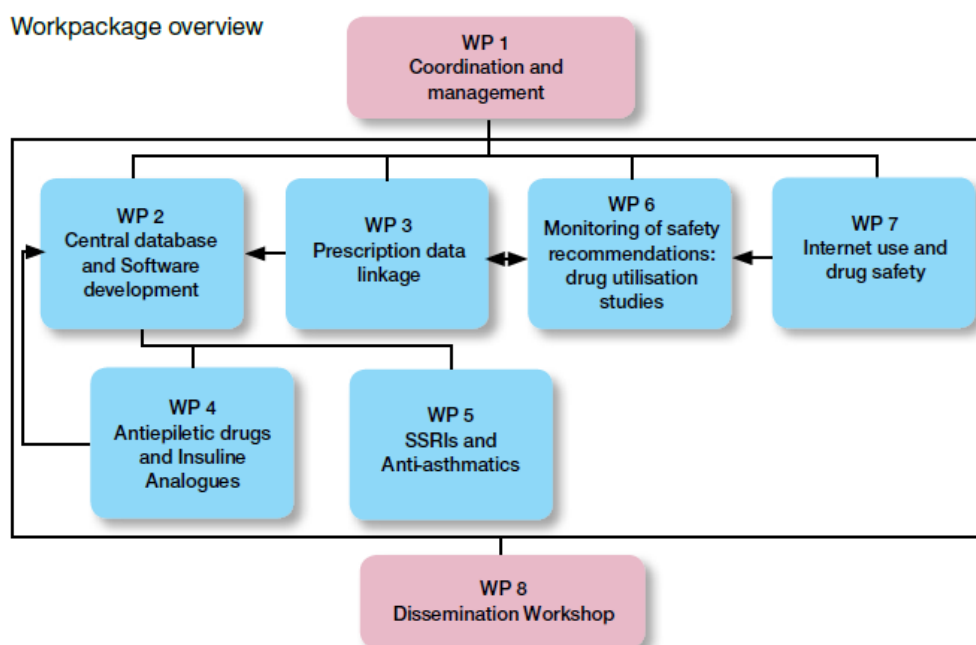


Figure 3.1: Work package structure of EUROMEDICAT

## 3.2 WP2 Central database and software development

### 3.2.1 Work undertaken

- EDMP software (EMDP, LDMP and DCMP) and manuals ready (**Deliverable 7**)
- Fully documented EUROmediCAT database ready for future pharmacovigilance studies (Dataset A, see **Table 3.1, Deliverable 8**)
- Development of Signal Detection methodology (**Deliverable 9**)
- Investigation of Signal Detection results (**Deliverable 10**)

### 3.2.2 WP2 results and foreground

#### Description of EUROCAT data made available for EUROmediCAT Central Database (Dataset A)

EUROCAT is a network of population-based registries for the epidemiological surveillance of congenital anomalies (CA) established in 1979. Each registry sends anonymised, uniformly coded data on cases of CA registered in the local population. Registries use the EUROCAT Data Management Program (EDMP) to transmit standardised data to a central database. Cases of congenital anomaly are all major structural congenital and chromosomal anomalies diagnosed prenatally or postnatally. These include livebirths, fetal deaths from 20 weeks gestational age (GA) and terminations of pregnancy for fetal anomaly. All registries in the network use a standardised methodology i.e. Standard variables, definitions, coding instructions (EUROCAT Guide 1.4 <http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Full-Guide.pdf>), data dictionary.

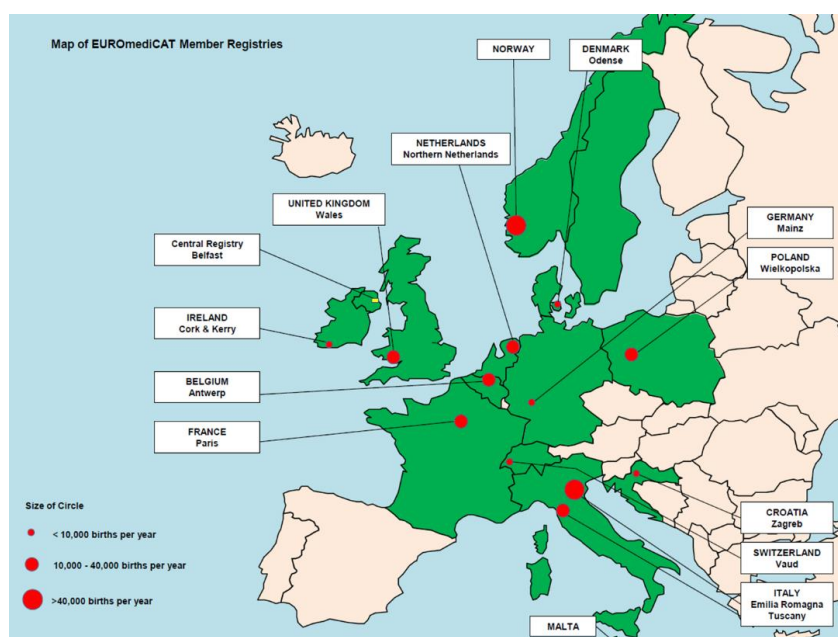
Common variables include:

- Baby: type of birth, sex, survival, gestational age
- Diagnosis: 8 malformations and syndromes coded in ICD10 with BPA extension
- Maternal illness exposure (both acute & chronic)
- Medication exposure
- Family history
- Possible confounders such as maternal age, parity, and in some registries: BMI, socioeconomic status, maternal education

EUROCAT regroups coded congenital anomalies into 89 standard subgroups, and has a standard list of minor anomalies for exclusion (EUROCAT Guide 1.4).

#### Design and software development

WP2 developed the EUROmediCAT central database (Dataset A, see **Table 3.1**) to collate uniformly-coded, validated data on cases of congenital anomaly, with information on maternal medication exposure during the first trimester of pregnancy, for 15 EUROCAT registries (**Figure 3.2**). The EUROmediCAT database built on the existing EUROCAT central registry database and the EDMP already used by local registries to transmit standardized anonymised data on congenital anomalies according to EUROCAT guidelines. Software developments were implemented in the central database and EDMP to improve



**Figure 3.2:** Map of EUROmediCAT Member Registries

coding of medication exposure data, including the provision of additional drug and maternal illness variables, as well as enabling 7 digit ATC drug codes to be entered for cases born before 2005, (**Deliverable 7**). Two new subgroups which group together aetiologically related congenital anomalies (laterality defects and neural crest defects) according to their ICD10 codes were approved by the EUROCAT Coding & Classification Committee and implemented in Dataset A.

A Prescription Linkage Program (LDMP) was developed and implemented in 5 registries with access to local prescription or administrative databases with information on prescriptions (**Deliverable 7**). Congenital anomaly data, extracted from Database A, was imported to LDMP which was then linked with local prescription/ administrative databases. This distributed database (Dataset B, see **Table 3.1**) enabled validation of registry medication data, and generated standard pre-defined tables on medication use associated with congenital anomalies which could then be combined for analysis. See Workpackage 3 for further description. A Diabetic Cohort Management Program (DCMP) was developed and implemented in 7 registries participating in a cohort study of diabetic pregnancies. Data relating to the mother and her offspring including maternal insulin exposure and glycaemic control was entered/ imported to DCMP by the participating registries (Database C). Malformed cases in DCMP were linked to cases in Dataset A (**Deliverable 7**). These software developments were essential for WP 3, 4 and 5. A data manual with instructions on how to run the new software was produced and uploaded to the website: “The EUROmediCAT Manual: User Instructions Relating to Work Packages 2-4”.

Whereas the original intention had been to create an additional dataset, “dataset D”, from the population cohort linkage studies, it became evident that due to data protection considerations, the population cohort linkage studies in Workpackage 5 would have to proceed by independent linkage and analysis of databases, followed by meta-analysis. No Dataset D was therefore created.

**Table 3.3: EUROmediCAT Registries contributing to Dataset A**

Registry	Years	Births (n)	CA cases (n)	CA cases with medication exposure (n)*
Antwerp (Belgium)#	1997-2012	308,067	7,693	512
Cork & Kerry (Ireland)	1996-2012	151,415	3,981	501
Emilia Romagna (Italy)**	1995-2012	595,214	12,323	2,846
Mainz (Germany)#	1996-2012	55,436	2,652	449
Malta#	1996-2012	71,620	2,196	402
N Netherlands#	1995-2012	340,310	9,038	3,976
Norway**	2005-2010	364,160	10,944	3,891
Odense (Denmark)**#	1995-2012	96,816	2,701	352
Paris (France)	2001-2012	319,636	10,279	1,106
Poland excluding Wielkopolska	1999-2010	3,228,380	49,383	13,962
Tuscany (Italy)**	1995-2012	505,101	11,054	1,435
Vaud (Switzerland)	1997-2012	120,397	4,716	487
Wales (UK)**#	1998-2012	501,720	19,370	3,240
Wielkopolska (Poland)#	1999-2010	440,096	11,787	3,310
Zagreb (Croatia)	1995-2012	120,403	2,104	257
Total		7,218,771	160,221	36,726

\*Excludes Vitamins, minerals and folic acid

\*\* Five registries also linking to prescription data for Dataset B, for a restricted time period (see WP3)

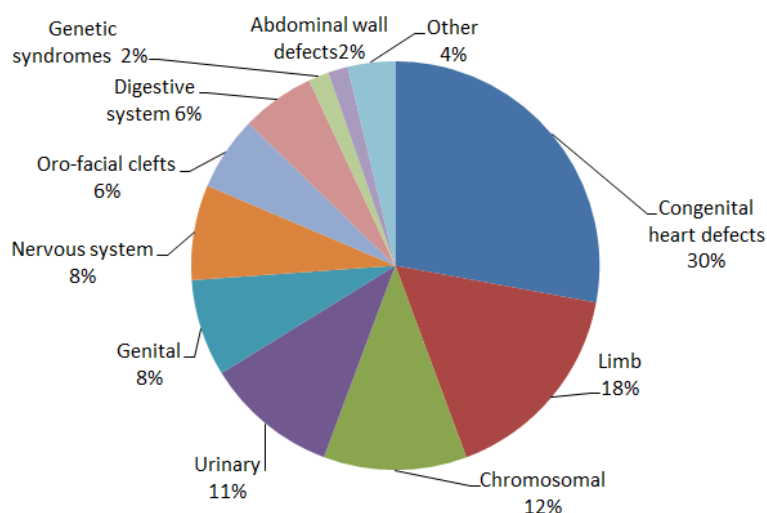
# Seven registries also linking to diabetic cohort for Dataset C, for a restricted time period (see WP4).

**Dataset A - establishment and documentation**

Fifteen EUROmedICAT registries covering a total population of 7.2 million births in the period 1995 to 2012 contributed to Dataset A (Table 3.3, Figure 3.2). There were 160,221 CA cases, defined as all major structural congenital and chromosomal anomalies diagnosed prenatally or postnatally (prevalence=221.9 per 10,000 births) of which 89% were livebirths (LB), 1% were fetal deaths from 20 weeks gestational age and 9% were terminations of pregnancy for fetal anomaly (TOPFA). Of the 160,221 CA cases, 36,726 had ATC-coded medication exposure information excluding Vitamins / Minerals / Folic Acid during the first trimester of pregnancy, which equates to a medication exposure prevalence of 229.2 per 1,000 CA cases (Table 3.3, Figure 3.2). Figure 3.3 shows the distribution of CA types.

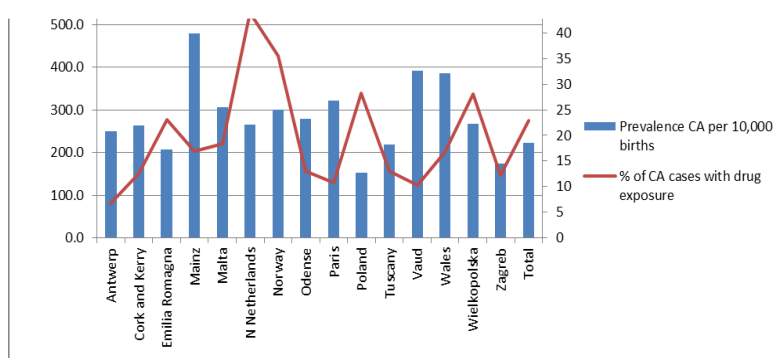
All registries except Poland and Zagreb have an overall CA prevalence of between 2 and 3%, but there are marked differences between registries in the proportion of CA cases with medication exposure information (Figure 3.4). A profile of each registry contributing medication exposure data to Dataset A was produced detailing information on how medication exposure information is collated within the registry. All registries except one accessed maternal records e.g. Obstetric, midwife, gynaecologist, delivery units, pregnancy pass; 9 registries accessed additional child health records e.g. paediatrician, geneticist, neonatologist, paediatric cardiologist /neurologist/ surgeon; 1 registry conducted maternal interview by clinician after birth; 1 registry accessed a prescription database and 1 was linked to the national prescription database. Consideration of data sources helps interpretation of differences in prevalence of medication exposure between registries (Deliverable 8).

Dataset A was used to conduct case malformed control studies in relation to medication exposure for new antiepileptic medications (WP4), Asthma medications (WP5) and SSRIs/antidepressants/psycholeptics (WP5). It was also used for systematic signal detection (WP2). Dataset A was linked to the Diabetic cohort (WP4) and to prescription databases (WP3).



**Figure 3.3:** Distribution of congenital anomalies registered in 15 EUROmedICAT registries.

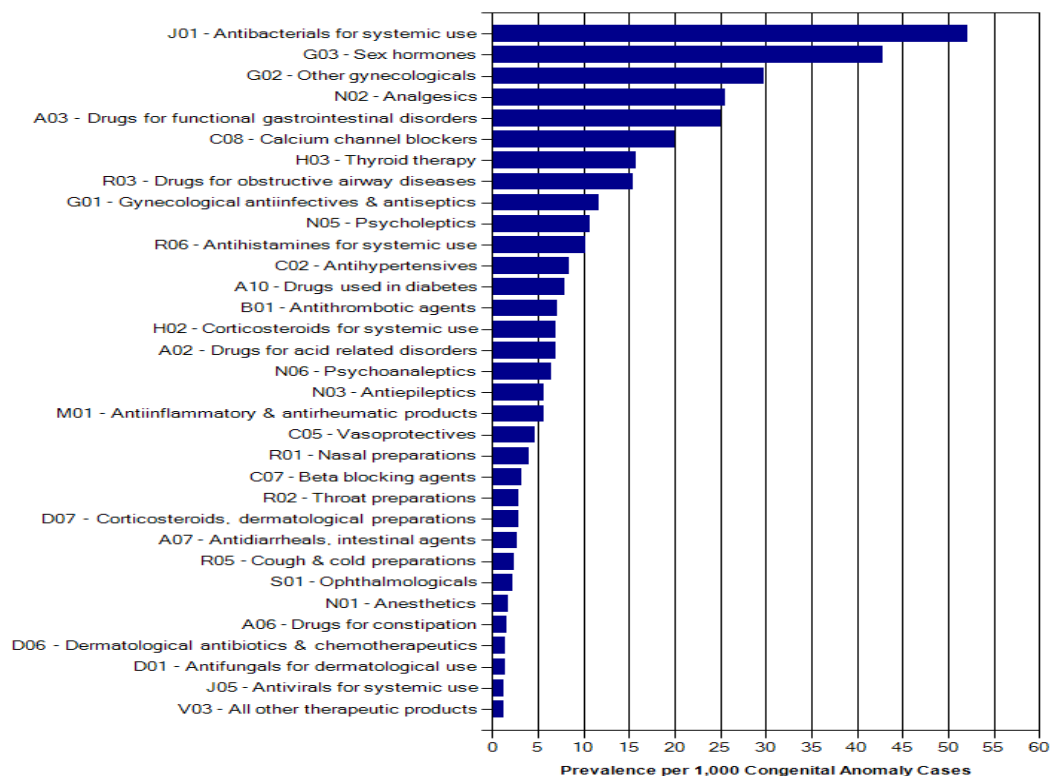
*\*An anomaly can occur in more than one organ group; however cases with chromosomal/ genetic syndromes are only included in the chromosomal and genetic subgroups*



**Figure 3.4:** Prevalence of congenital anomalies per 10,000 births & proportion of congenital anomaly cases with medication exposure\*, per EUROmedICAT registry, 1995-2012

### Pharmacovigilance data summary and signal detection

WP2 developed EUROmediCAT interactive tables showing the frequency and prevalence of medications recorded in the EUROmediCAT central database by registry, year of birth and type of birth. The tables are restricted to the members-only section of the website for network use. The user can choose the level at which ATC codes are viewed up to the full fifth level for individual medicines. The feasibility of conducting studies of rare medication exposures of current interest can be determined from these tables as they provide a quick summary of rare medication exposures in the dataset.



**Figure 3.5:** Prevalence of medication exposures in Dataset A by type of medication

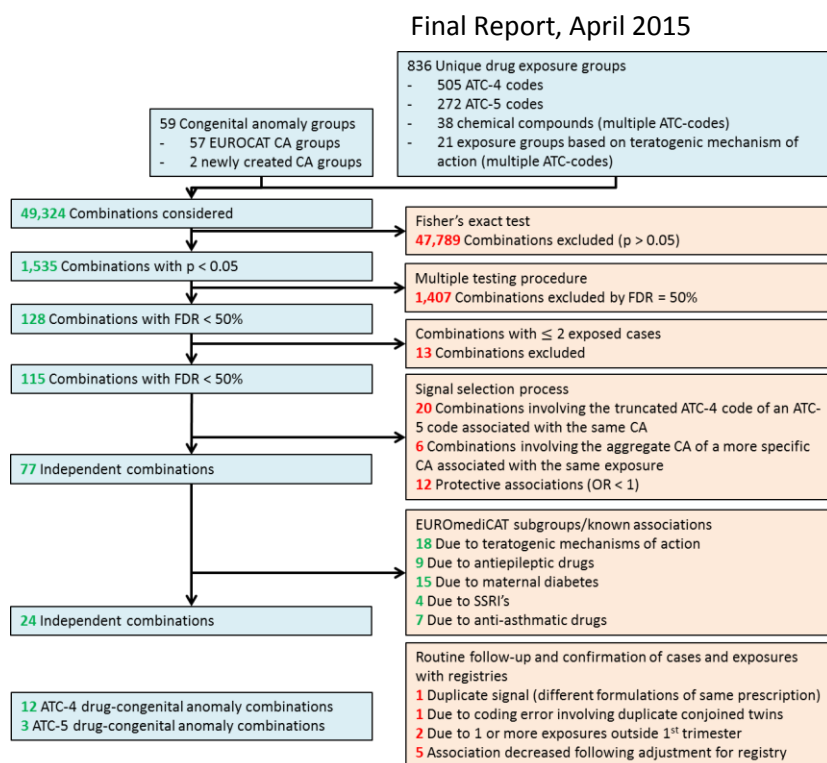
Dataset A was used for general pharmacovigilance (signal detection and signal evaluation) to identify potential new teratogens based on population surveillance. A pilot study based on a 25% sample of cases exposed to medications extracted from Dataset A determined that a False Discovery Rate (FDR) of 50% was appropriate for EUROmediCAT systematic signal detection. Following the pilot study, the signal detection process was further refined for use as a routine system, as recommended by EMA<sup>1</sup>, and the methodology documented (**Deliverable 9**). Analysis, comparing the odds of exposure of a specific CA and drug was compared to the odds of exposure to the same drug in the remainder of the dataset using a 1-sided Fisher's exact test.

Following exclusions, the final pharmacovigilance dataset consisted of 14,950 malformed babies. Analysis was conducted on 59 CA subgroups and 836 unique ATC drug exposures, which generated 77 potential signals (**Figure 3.6**). Eighteen of these were related to groups of ATC codes relating to teratogenic mechanisms of action, and 35 were related to new anti-epileptic drugs, Insulin analogues, anti-asthmatics and SSRIs (anti-depressants) and were forwarded to the relevant WP4 and WP5 leaders responsible for conducting risk assessment studies related to these medications. The remaining 24 potential signals were subject to a detailed investigation.

<sup>1</sup> Committee for Medicinal Product for Human Use. Guideline on the exposure to medicinal products during pregnancy: need for Post-authorisation data. EMEA/CHMP/313666/2005

Of the 24 original ‘other’ potential signals, 9 were discarded following verification of the data and detailed follow-up investigations, which left 15 validated potential CA-drug exposure signals related to gastrointestinal drugs (4), antihypertensives (n=2), female sex hormones (n=3), drugs used in infertility treatments (n=2), antiretrovirals (n=2), selective serotonin (5HT1) agonists (n=1) and detoxifying agents for anti-neoplastic treatment (n=1). An extensive literature review was conducted, using also specialist reproductive toxicity databases. Eight of these signals had no prior supporting evidence and require confirmation in an independent dataset. A further 7 signals had some prior supporting evidence and should be prioritised for further investigation before being further evaluated in relation to

clinical decision making. A full report of the methodology and the generated signals was produced (**Deliverable 10**) and will be disseminated as two scientific papers.



**Figure 3.6:** Flowchart of CA-medication exposure combinations in pharmacovigilance signal detection

### 3.3 WP3 Prescription data linkage

#### 3.3.1 Work undertaken

- Linkage of prescription data to CA data (**Deliverable 11**)
  - Development of the Linkage Data Management Program (LDMP) software
- Prescription linkage report (**Deliverable 12**)
- Scientific paper on methodology and results of prescription data linkage (**Deliverable 13**)

#### 3.3.2 WP3 results and foreground

The main objective of WP3 was to link electronic prescription data to congenital malformation registers to improve the information on medication exposure in the malformation registers. The linked data will be utilised in WP5.

##### Prescription data linkage (dataset B)

Due to data confidentiality regulations, registries in Wales and Denmark were not allowed to send the linked case data outside their protected digital environment (server). Therefore, we applied a distributed database model in which the linked datasets were kept at the individual registries. This distributed database model replaced the intended central dataset B. CA cases born between 1998 (or first year available in the prescription database) and 2010 were included in data linkage. Linkage was performed by matching personal identification numbers or maternal characteristics. In the **deliverable 11** report, the methodology of the linkage, the structure and the contents of the linked datasets are described.

The linked datasets consist of a master table with data on the malformed cases derived from the CA register and transformed to the EUROCAT format and a table with prescription data. Additional variables were added to the master file to indicate if the mother was identified in the prescription database. The table with prescription data is a relational table; therefore there is no maximum on the number of prescriptions per case. Required variables from the prescription data were ATC code of the prescribed medication and date of prescription. Optional variables included name of the medication, amount prescribed and daily dose prescribed.

### **Software development**

An Access-based software module, the Linkage Data Management Program (LDMP), was developed to ensure a validated dataset B. The LDMP includes functions to import and export data, validate data and generate tables for evaluation and analyses. The LDMP builds further on the EUROCAT Data Management Program (EDMP), which was used by all registries to ensure a validated CA dataset B. The use of the LDMP ensured the compatibility of anomaly subgroups and medication groups among participating registries. First trimester exposure was defined as a prescription with the date of prescription between 0-97 days after LMP. For certain analyses the period for first trimester exposure was extended to include the 31 days before LMP. The functions of the LDMP are described in the EUROmedicAT manual. Case selection and predefined tables were generated through the LDMP. The tables were sent to the coordinator of the WP to be analysed centrally.

Odense, Denmark was not able to use the LDMP as the use of special software is not allowed on the server of Statistics Denmark. In addition, only the four medication groups of main interest in the EUROmedicAT project were included in the linkage in Odense because of the costs associated with using the data. The data from the CA register in Odense was validated through the EDMP. The prescription data was validated manually by an experienced statistician and medication subgroups and exposure periods were created according to the definitions in the linkage protocol. The required tables were generated manually, using the same selection criteria and definitions as in the LDMP. The results of the prescription data linkage are extensively described in the report on prescription data linkage (**deliverable 12**).

### **Linkage rate**

A total of 52,619 cases of CA were present in the five CA databases. Linkage was possible for 65.6% of these cases. The linkage success varied per registry, from (almost) 100% in Odense and Norway to 32% in Wales. In Wales linkage was not possible for all pregnancies, as the primary care practices that supply the prescription data cover only 40% of the population. Therefore the prescription database did not cover 100% of the population. Emilia Romagna could not include TOPFA cases in the linkage, since the identification number used for linkage is only given at birth. The CA registry in Tuscany could recover the ID number for 52% of the mothers. Foreign born women were less likely to have their ID number recovered.

### **Maternal and case characteristics between linked and non-linked cases**

For the registries that could not link all CA cases to the prescription database (Wales, Norway, ER and Tuscany), possible differences in characteristics between linked and non-linked CA were examined. There was a correlation between year of birth and linkage for all registries. Type of birth, maternal age and certain types of defects differed significantly between linked and non-linked cases for Tuscany and ER. Maternal age differed also between linked and non-linked cases in Wales and Norway.

**First trimester exposure rates**

It should be noted that the CA registers already contained some medication exposure data pre-data linkage to prescription databases. In general, first trimester exposure rates for antiepileptic medication, insulin analogues and antiasthma medication were comparable between the prescription databases and the pre-linkage CA data.

Differences in prescription rates between registries can be attributed to prescribing differences between regions. For the SSRIs the first trimester exposure rate according to the prescription data was 3 times higher than according to the CA register data in Wales and Tuscany. The exposure rates for antibiotics according to the prescription data were much higher than the exposure rates according to the CA register data for all databases. Except for Wales, the exposure rates for gonadotropins were higher in the prescription data than in the CA register data.

**Agreement between medication recorded in CA registers and prescription databases**

Despite comparable first trimester exposure rates among CA registers and prescription databases, agreement between these two data sources may be low as the exposures can be recorded in different pregnancies. For medicines that are taken for chronic conditions such as epilepsy and diabetes, agreement according to the prescription data is high, above 60% (except for antiepileptic medication in Emilia Romagna), meaning that >60% of the cases who received a prescription for antiepileptic medication or insulin analogue in the first trimester also were exposed according to the CA register data. The agreement, both according to prescription data and CA register data for asthma medication is lower than for antiepileptic medication. A possible explanation is that certain asthma medication is only taken when necessary, so that a prescribed medicine can be used even months after prescription. For SSRIs, the agreement according to the prescription data is lower than according to the CA data. This means that if exposure to an SSRI is recorded in the CA data, usually a prescription in the first trimester is recorded in the prescription data, whereas if a prescription in first trimester is recorded in the prescription data, the exposure is not always recorded in the CA data. For antibiotics and gonadotropins the agreement for both data sources is low.

Extending the first trimester definition in the prescription data to include the month before the start of the pregnancy (-31 days to 97 days) did not influence the agreement for antiepileptic medication and insulin analogues, but did increase the agreement according to the CA data for antiasthma medication and SSRIs.

**Actual use of prescribed medication**

As part of this WP we performed a cross-sectional study embedded in the Northern Netherlands CA registry. In this study we investigated to what extent prescription data reflect the actual use of medication, prescribed during pregnancy. Compliance rates were calculated for several medication groups as the number of mothers that had taken the medication divided by the number of mothers to which the medication had been prescribed. Compliant use was defined as the mother confirming she took the medication, even when she received multiple prescriptions from the same medication group and took only one. In addition, we determined for each prescription that was taken, whether the medication administered conformed to prescribed dosage and duration. During the first trimester the compliance rate ranged from 0.83 for medication for chronic diseases and 0.92 for medication for pregnancy related symptoms. Most of the actually used medications were used according the dosage and duration prescribed, and if not, the used dosage and duration was lower than prescribed. Therefore we conclude that studies using prescription data will most likely overestimate exposure. However, this overestimation seems

minimal which makes prescription records a reliable source in research on associations between medication use in pregnancy and congenital malformations.

### 3.4 WP4 Antiepileptic drugs and insulin analogues

#### 3.4.1 Work undertaken

- Creation of diabetic cohorts and linkage to CA registers (Dataset C, see **Table 2.1; Deliverable 14**)
- Literature review and case-malformed control study on the risk of specific CA in relation to new AEDs (**Deliverable 15**)
  - Study of risk of congenital anomaly in relation to exposure to the second generation AED topiramate
- Literature review on the risk of specific CA in relation to insulin analogues (**Deliverable 16**)
- Diabetic cohort study investigating the relationship between specific CA and insulin analogues (**Deliverable 17**)

#### 3.4.2 WP4 results and foreground

The main objective of WP4 was to assess the relationship between AEDs and insulin analogues and congenital anomalies. This process was initiated by extensive literature reviews to search for signals of specific congenital anomalies in relation new AEDs (vigabatrin, oxcarbamazepine, felbamate, lamotrigine, topiramate, gabapentine, levetiracetam, pregabalin and zonisamide) and insulin analogues (lispro, aspart, glulisine, glargine, degludec and detemir). The signals of specific congenital anomalies associated with AED use found in these literature searches, were further evaluated in the EUROCAT database using a case-malformed control study (signal evaluation). No signals were detected for insulin analogues compared to human insulin use and therefore no signal evaluation was involved in the diabetic cohort study.

##### Literature review of new antiepileptic drugs

This literature review aimed to collect signals indicating an association between a new AEDs and specific congenital anomalies. Any strong signal will be investigated further in a case-malformed control study using the EUROCAT AED database as part of a signal evaluation process.

Pubmed and Embase were systematically searched for studies with pregnancies exposed to new AEDs in relation to specific congenital anomalies. The anomalies found were classified according to the EUROCAT classification. The prevalence of specific congenital anomalies of fetuses exposed to individual AEDs of the combined studies were calculated and compared to the prevalence of the general population. A significant higher prevalence based on two or more cases among the exposed fetuses was considered a signal. Eight signals related to either lamotrigine or topiramate monotherapy were found of whom only the signal of topiramate and cleft lip with or without cleft palate could be evaluated as strong evidence. For levetiracetam, gabapentin and oxcarbazepine no signals were found. The other 11 new AEDs had few or no exposed pregnancies in this literature review.

Conclusions from the study: We concluded that the signal of topiramate and cleft lip with or without cleft palate should be further evaluated (**Deliverable 15** part a).

##### Evaluation of the signal Topiramate and orofacial clefts

*We evaluated the signal for Topiramate and risk of orofacial clefts found in the literature review as part of signal evaluation. Topiramate is licensed for use both in treatment for epilepsy and migraine and the use has increased among pregnant women.*

To assess the risk of orofacial clefts (OCs) in infants whose mothers had taken Topiramate during the first trimester of pregnancy we performed a population-based case-control study with malformed controls using the EUROCAT AED Database. This database including data from 19 population-based registries of congenital anomaly in Europe with a total coverage of 8.0 million births from 1995 to 2011. Cases were 10,802 nonsyndromic OC registrations, of whom 8,919 were isolated; and 6,827 were cleft lip with or without cleft palate (CL/P). Controls were 136,838 nonchromosomal, non-OC registrations. We compared first trimester Topiramate use vs no-AED use, for mono and polytherapy. Exposure to Topiramate monotherapy was recorded for a total of 12 registrations, with 1 registration in the case group (isolated cleft palate) and 11 in the control group (OR 1.15, 95% CI: 0.03-7.93 for OC relative to other malformations and OR 4.02, 95% CI: 0.09-27.7 for isolated cleft palate). There was no registration of CL/P in Topiramate monotherapy exposure. There were 36 registrations with Topiramate polytherapy exposure, of whom 6 with isolated CL/P, 3 with cleft palate and 27 in the control group. Out of 36 of Topiramate polytherapy, 19 included valproic acid, 8 included carbamazepine and 4 included lamotrigine. The unadjusted ORs for TPM polytherapy vs no AED use was 4.23 (95% CI 1.75- 9.26) for OC, 4.36 (95% CI 1.31- 11.5) for isolated CL/P and 3.27 (95%CI 0.38- 13.0) for isolated cleft palate. The risk estimation of OCs, CL/P or cleft palate in relation to Topiramate monotherapy/polytherapy did not change when adjusted for maternal age or region.

Conclusions from the study: Our study did not show a specific increased risk of OCs relative to other malformations due to first trimester Topiramate monotherapy exposure. The prevalence of Topiramate monotherapy exposure was five times lower in our data than reported in the United States which limited our ability to confirm or refute previous findings. First trimester use of Topiramate polytherapy was associated with CL/P. The present data should be interpreted with caution due to the small sample size and wide confidence interval. The observed association of Topiramate polytherapy exposure with increased risk of CL/P needs to be confirmed by others. However, we should keep the absolute risk in perspective. Approximately 1 in 1000 infants is born CL/P; assume our results are valid, our observed OR of approximately 4 would lie to translate into a risk in the order of 4 per 1000 Topiramate -exposed pregnancies. The teratogenic risk should be balanced against the risk of alternative therapeutic choices (others AEDs among others valproic acid and carbamazepine) as well as the comparative effectiveness of Topiramate treatment (**Deliverable 15** part b).

### Literature review insulin analogues

Insulin analogues are now commonly used in diabetic pregnant women. Diabetic pregnancies, especially in case of pre-gestational diabetes, have higher risks of congenital anomalies. To avoid additional risks in diabetic pregnancies, it is important to know whether the exposure to insulin analogues in pregnancy has any higher risk of specific congenital anomalies in the offspring than exposure to human insulin. Therefore we performed a literature review to investigate the risk of specific congenital anomalies among diabetic pregnancies, exposed in the first trimester to insulin analogues, compared to human insulin.

We searched Pubmed and Embase for articles meeting the following inclusion criteria:

- original, non-overlapping studies including pregnancies of women with pregestational diabetes
- exposure to insulin lispro, aspart, glulisine, glargine, detemir or degludec in the first trimester (<12 weeks of gestation)
- detailed information on congenital anomalies
- randomized controlled trials, cohort studies or observational studies with  $\geq 5$  exposed pregnancies

The studies were analysed to compare the rate of infants with congenital anomalies among insulin analogues exposed pregnancies with human insulin exposed pregnancies. We compared the prevalence of specific major malformations, by reclassification according to the congenital anomaly subgroups of EUROCAT. A significant higher risk of a specific congenital anomaly among fetuses exposed to insulin analogues compared to human insulin was considered as a signal. We found 32 studies: 2 randomized controlled trials, 16 cohort studies and 14 observational studies of pregnancies exposed to insulin lispro, aspart, glargine or detemir. No studies were found on insulin glulisine or degludec.

No significant difference was found in the anomaly rate among fetuses exposed to lispro, aspart, glargine and detemir compared to human insulin (respectively Relative Risk= 0.88 (95% CI 0.60-1.28), 0.92 (0.37-2.29), 0.73 (0.38-1.40), and 0.91(0.35-2.39)). The prevalence of specific congenital anomaly subgroups was not significantly higher in insulin analogues exposed fetuses compared to human insulin exposed fetuses. The congenital anomalies found were known as associated with diabetes in pregnancy and the prevalences were comparable to those found in the general diabetic pregnant population.

Conclusions from the study: In this literature review no increased risk of specific congenital anomalies was found among the offspring of women with pre-gestational diabetes exposed to insulin analogues in the first trimester of pregnancy compared to human insulin exposure.

### **Diabetic cohort study**

Insulin analogues have been available on the market since the mid- 1990s and it is known from clinical and experimental data that insulin analogues result in improved glycemic control, fewer hypoglycemic episodes and improved patients satisfaction. In this context, insulin analogues may be particularly useful in pregnancy. The use of insulin analogues in pregnancy is increasing in Europe (see WP6), but information on teratogenic risks is lacking. It is not clear whether insulin analogues use in pregnancy is related to any risk of congenital anomaly (CA). Insulin analogues may decrease the risk of diabetes-associated malformations by promoting better glycemic control (HbA1C-value), or increase the risk of these or other CA through specific effects relating to the pharmacological properties of analogues. Available studies on insulin analogues during pregnancy are not sufficiently powered to evaluate the risk of specific major CA. We evaluated the risk of major congenital anomalies associated with insulin analogues use in women with pre-gestational diabetes.

A population-based cohort of pre-gestational diabetic pregnancies (dataset C) was established retrospectively using medical records from 7 European regions (Denmark, Germany, Malta, Antwerp, Northern Netherlands, Wales) covered by EUROCAT congenital anomaly registries and linked to the malformation register. A total of 1,877 births to women with pre-gestational diabetes were enrolled in the study during 1996-2012. During the first trimester, 870 births (46.3%) were exposed to only human insulin, 397 births (21.2%) to only insulin analogues, 394 births (20.1%) to both human insulin and insulin analogues. The proportion of still birth and spontaneous abortion (4.0%) are higher among only insulin analogue group compared to only human insulin group (1.4%). Overall, 132 births (7.0%) with major congenital malformation were detected, of which 7 were chromosomal. The prevalence of major congenital anomalies in births exposed to only insulin analogues (3.8%) during the first trimester was significantly lower than those exposed to only human insulin (8.6%); relative risk = 0.42 (95% CI: 0.24-0.73). This is largely due to the decreased prevalence of non-chromosomal congenital heart defects (CHD): relative risk = 0.18 (95% CI: 0.05-0.58). This decreased prevalence remained after adjusting for glycaemic control and region. The prevalence of non-CHD congenital anomalies among births exposed to only insulin analogues in

the first trimester (3.0%) was also lower than those exposed to only human insulin (4.0%), but not statistically significant.

Conclusions from the study: This study shows that first trimester exposure to insulin analogues did not increase the risk of congenital anomalies compared to exposure to human insulin. The decrease risk of CHDs among the insulin analogues exposed provides a further piece of evidence of the safety of insulin analogues with regards to CA. The higher risk of fetal death in relation to insulin analogues warrants further investigation.

## 3.5 WP5 SSRIs and anti-asthmatics

### 3.5.1 Work undertaken

- Report to CHICOS WP1 regarding potential of birth cohort data for drug teratogenicity studies (**Deliverable 18**)
- Case-malformed control study on risk of specific CA in relation to anti-asthmatics (**Deliverable 19**)
  - Literature review on risk of specific CA in relation to anti-asthmatics
- Case-malformed control study on risk of specific CA in relation to SSRIs (**Deliverable 20**)
  - Literature review on risk of specific CA in relation to SSRIs
- Population linkage study on risk of specific CA in relation to SSRIs (**Deliverable 21**)
- Population linkage study on risk of specific CA in relation to anti-asthmatics (**Deliverable 22**)

### 3.5.2 WP5 Results and foreground

The main objective of WP5 was to assess the relationship between anti-asthmatics, SSRIs and congenital anomalies. WP5 also explored the potential of the European birth cohorts participating in the FP7 funded CHICOS project for drug teratogenicity studies.

#### Evaluation of other databases – birth cohort studies

An online survey was conducted regarding the congenital anomaly data and medication exposure data currently available in European birth cohorts participating in the FP7 funded CHICOS project. Twenty-seven cohorts were invited to complete the survey, 24 responded of which 12 cohorts had both medication and congenital anomaly data and were potentially interested to join a collaborative effort. These 12 cohorts cover 238,000 births, 87% of which are from two large cohorts (The Danish and Norwegian cohorts close to 100,000 births each). The report of this survey was made available to the CHICOS project in February 2012 (**Deliverable 18**).

A second additional phase of the survey was done in addition to the deliverable. In this phase the 12 cohorts with medication and congenital anomaly data were invited to submit their congenital anomaly data for evaluation of its quality (coding precision, completeness of ascertainment), as well as the prevalence in the cohort of three exposures in the first trimester of pregnancy (anti-depressants, anti-asthmatics, fever). Of the 12 cohorts, 6 have sent the requested data and 1 has sent partial data which have been analyzed and assigned EUROCAT subgroups. 5 cohorts have declined to continue in the study or have been unreachable. For those participating, it was found that there was much to be done to standardize the coding and classification of congenital anomalies to allow further analysis, with suggestions given for study protocols.

#### Risk of congenital anomalies in relation to anti-asthmatic use: case-malformed control design

The literature review detected 9 signals for first trimester fetal exposure to beta-2-agonists and 4 signals for fetal exposure to corticosteroids. Beta-2-agonists were associated with spina bifida, cleft lip and palate,

cleft palate, severe CHD, Tetralogy of Fallot, esophageal atresia, anal atresia/stenosis, gastroschisis and omphalocele. Corticosteroids were associated with cleft lip and palate, cleft palate, anal atresia/stenosis and hypospadias. The case-malformed control study including data from 13 registries confirmed the association for cleft palate and gastroschisis with fetal exposure to inhaled beta-2-agonists. None of the 4 signals for inhaled corticosteroids were confirmed.

Conclusions from the study: Even though the increased risk of cleft palate and gastroschisis associated with exposure to inhaled beta-2-agonists is statistically significant, it does not present a large added risk for each individual pregnancy. Cleft palate has a prevalence of about 1 case per 1000 births, gastroschisis of 2-3 per 10,000 births. Even with a five-fold increased risk (as compared to the less than twofold increase in odds observed) the risk for the individual pregnancy would still be below 1 in 100.

We did not find any statistically significant increase in risk of congenital anomalies after exposure to inhaled steroids. This is reassuring, as maternal asthma and asthma exacerbation have been associated with an increased risk of congenital anomaly and of other negative pregnancy outcomes for both mother and infant. Use of prophylactic inhaled steroids to prevent asthma exacerbations and reduce the need for beta-2-agonists may be the best solution for treatment of asthma in pregnancy (**Deliverable 19**).

#### **Risk of congenital anomalies in relation to SSRI use: case-malformed control design**

The use of selective serotonin reuptake inhibitors (SSRI: ATC code N06AB) has risen over the past few decades. The safety of these drugs when used in pregnancy has been questioned, including their effect on fetal organogenesis when taken in the first trimester of pregnancy. SSRI are often co-prescribed with other types of medication: antidepressant medications (4% in our data) and with psycholeptic medications (16% in our data). We therefore expanded our study to include all antidepressants (ATC code N06A) and psycholeptic medications (N05A) including anti-psychotics (ATC code N05A), anxiolytics (ATC code N05B) and sedative/ hypnotic type medications (ATC code N05C).

The literature was reviewed, identifying 16 signals, where at least one study had found a statistically significant association between an antidepressant used in the first trimester of pregnancy and congenital anomaly: Congenital Heart Defects (CHD), Neural Tube Defects (NTD), Anencephaly (a specific NTD), Eye anomalies, Ear/Face/Neck anomalies, Respiratory anomalies, Digestive System anomalies, Ano-rectal malformations, Gastroschisis, Omphalocele, Renal dysplasia, Limb reduction anomalies, Lower limb reduction anomalies, Clubfoot, Craniosynostosis and Cleft palate.

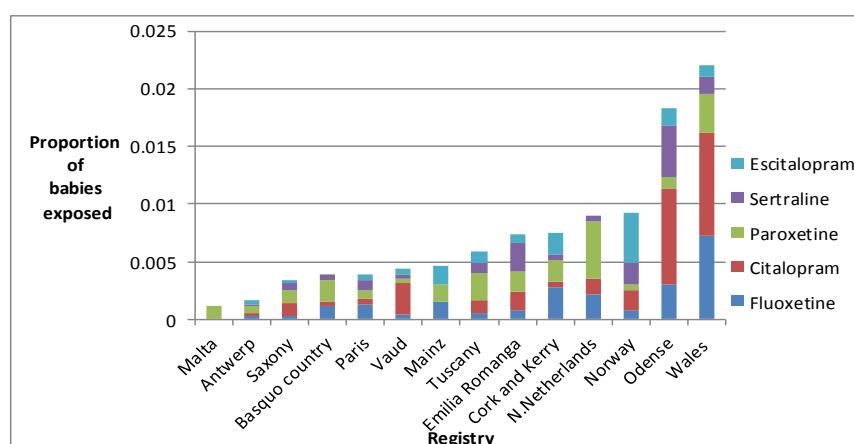
We used data from 14 EUROCAT congenital anomaly registries in 12 countries covering a total population of over 3 million births. Four of the registries provided data enhanced through data linkage to maternal medication prescriptions (see Workpackage 3), contributing 50% of the antidepressant/psycholeptic exposures. SSRI use recorded for babies with congenital anomaly is shown in **Figure 3.7**. We confirmed that there is evidence of a small excess risk, of borderline statistical significance, of CHD associated with SSRI use in the first trimester of pregnancy, particularly severe CHD. We found new evidence that this relates to citalopram which has recently been more commonly prescribed in the European population than paroxetine and fluoxetine. We found a statistically significant excess risk of Ebstein's anomaly relating not only to SSRI but all antidepressants and psycholeptic groups studied, of particular interest given previous evidence relating to lithium and benzodiazepines. We also found that there is evidence of excess risk of non-CHD signal anomalies associated with use of SSRI or specific SSRI, specifically for NTD, anophthalmos/microphthalmos, respiratory anomalies, gastroschisis, hypospadias, renal dysplasia and club

foot. We found no evidence to confirm signals in the literature for craniosynostosis, omphalocele or limb reduction anomalies with SSRI exposure consistent with the signals found in the literature. Our study had less statistical power for non-SSRI antidepressants or psycholeptics which were less frequent exposures, but some associations based on a small number of cases are worthy of follow-up. We did not find evidence of large excess risks associated with antipsychotics or other psycholeptics, nor with non-SSRI antidepressants. There was some evidence that combinations of SSRI and of SSRI and non-SSRI antidepressants were associated with higher risks of CHD and non-CHD anomalies which requires further research. Unfortunately, dose information was not available.

Conclusions from the study: There was no clear evidence that one type of SSRI is preferable to another in terms of safety, but rather evidence that congenital anomaly risk is found across all SSRI types studied. The increased risk, if causal, is small for individual mothers, but reinforces the need to assess appropriate use of these medications to make sure that benefits outweigh harm (**Deliverable 20**).

### Risk of congenital anomalies in relation to SSRI use: cohort linkage design

We investigated the putative teratogenicity of SSRI exposure in the quarters preceding and following 1<sup>st</sup> day of last menstrual period (LMP) by analysing prospectively collected electronic healthcare data including prescriptions for all pregnant women linked to three population based congenital anomaly registries which are members of EUROCAT – Norway (2004-2010), Wales and Funen (2000-2010), Denmark (2000-2010).



**Figure 3.7:** Breakdown of SSRI use as proportion of babies with CA, per EUROmedicat registry

We identified 519,117 deliveries with data covering pregnancy and the preceding quarter, and 462,641 with data covering pregnancy and one year either side. Prescription of SSRIs 91 days either side of LMP was associated with: a non-significant increase in the overall prevalence of congenital anomalies (3.09% [400/12,962] vs. 2.67% [13,536/506,155] odds ratio (OR) 1.09, 95% confidence interval 0.99 - 1.21); marginal difference in all congenital heart defects (CHD) (0.93% [121/12,962] vs. 0.89% [4503/506,155] OR 1.03, 0.86-1.24) and an increased risk of severe CHD (34/12,962 [0.26%] vs 865/506,155 [0.17%] OR 1.50, 95%CI: 1.06 - 2.11). Prescription of high dose tablets or capsules or >1 prescription further increased the risk of severe CHD, to 0.49% (7/1429, meta-regression OR 1.49, 1.12-1.97) and 0.31% (20/6392, OR 1.98, 1.26 - 3.10), consistent with an SSRI-exposure related risk. Exploration of confounding by indication (underlying depression) or associated socioeconomic or lifestyle exposures found no evidence that these explained the excess risk of severe CHD.

Conclusions from the study: By employing a population cohort linkage approach, we have shown that the overall risk of CA is very small, but that the excess risk of severe CHD with SSRI exposure is a robust finding. (**Deliverable 21**)

**Risk of congenital anomalies in relation to anti-asthmatic use: cohort linkage design**

The study included data from Wales, Norway and Funen County in Denmark using the same databases as in Deliverable 21. The study confirmed the association of inhaled steroids with anal atresia found in the literature and found potential new associations with combination treatment (inhaled long-acting beta-2-agonists and inhaled corticosteroids): severe CHD and common AV canal. The study is not able to distinguish between the effect of maternal asthma and asthma medication use. The potential new associations should be interpreted with caution due to the large amount of comparisons performed in this study (**Deliverable 22**).

**3.6 WP6 Monitoring of safety recommendations: drug utilisation studies****3.6.1 Work undertaken**

- Spreadsheet with national guidelines relating to prescription of anti-asthmatics, AEDs, insulin analogues and SSRIs in European countries (**Deliverable 23**)
- Study on use of healthcare databases for drug safety in pregnancy studies (**Deliverable 24**)
- Study on effectiveness of pregnancy prevention programs for teratogenic drugs in Europe (**Deliverable 25**)
- Drug utilisation study on use of antidepressants during pregnancy in Europe (**Deliverable 26**)
- Drug utilisation study on use of AEDs during pregnancy in Europe (**Deliverable 27**)
- Drug utilisation study on use of antidiabetic medicines during pregnancy in Europe (**Deliverable 28**)
- Drug utilisation study on use of anti-asthmatics during pregnancy in Europe (**Deliverable 29**)

**3.6.2 WP6 Results and foreground**

The main objective of WP6 was to conduct drug utilisation studies for antidepressants, AEDs, antidiabetics and anti-asthmatics in pregnant women in Europe. WP6 also collected prescription guidelines of these medicines in European countries and conducted a study on use of healthcare databases for drug safety in pregnancy studies.

**Drug utilisation studies in relation to pregnant women**

To our knowledge these were the first studies to include pre- and post-pregnancy prescribing in multiple areas of Europe. A common protocol was implemented, accessing databases in Denmark, Norway, The Netherlands, Italy (Emilia Romagna/Tuscany), Wales, and the Clinical Practice Research Datalink, representing the rest of the UK. The UK databases captured all prescriptions issued and the non-UK databases captured prescriptions actually dispensed. The study captured over 1.2 million pregnancies and demonstrated that regional differences exist in the prevalence of prescribing to women during and surrounding pregnancy for all four medicine classes under study. Regional differences were also observed in national prescribing guidelines and the specific products within each medicine class most commonly prescribed. In addition, inconsistencies were identified between prescribing practices and what is recommended in the guidelines or known from the scientific literature.

**For SSRIs**, the study found marked differences in the extent of SSRI prescribing to women before, during and after pregnancy (**Figure 3.8**). Considerably higher levels of prescribing were observed in the UK compared with Denmark, the Netherlands and Italy and the higher pre-pregnancy prescribing in the UK resulted in higher first trimester exposures. SSRI prescribing was at its lowest in all databases during the second and third trimesters of pregnancy. After pregnancy, SSRI prescribing increased more rapidly in the UK databases than other regions and unlike the other regions, the post-pregnancy prevalence of use in the UK was considerably higher than pre-pregnancy. Fluoxetine and citalopram were the SSRIs of choice during pregnancy in Denmark and the UK databases, whilst in Italy and the Netherlands, despite studies in the

literature reporting an increased risk of congenital heart defects and other anomalies, paroxetine was more commonly prescribed.

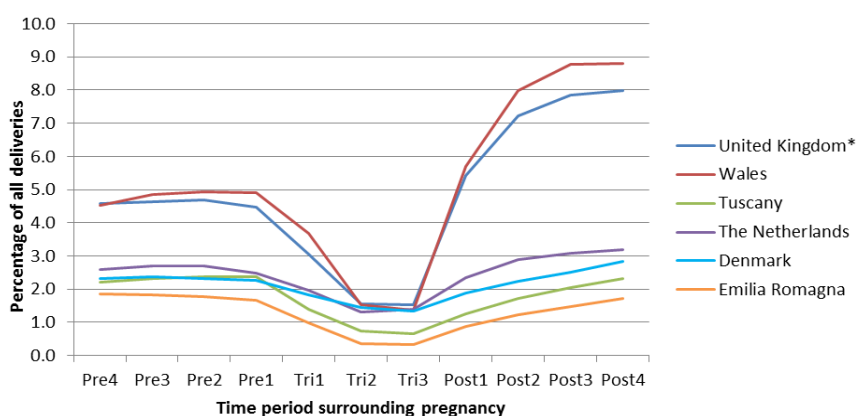
The variations observed in the type and extent of SSRI prescribing indicates an absence of European consensus on prescribing to pregnant women and women of childbearing age. When a woman becomes pregnant, the benefit-risk profile of SSRI medicine changes and this was evident from the reduction in SSRI use observed in all European regions during pregnancy. Further research should investigate whether women with mild depression in regions with higher SSRI prescribing are being inappropriately prescribed antidepressants during pregnancy, deriving no established benefit but exposing the fetus to possible risk.

**For antiepileptics**, geographic variations were identified in the prevalence of AED prescribing, however, in all regions prescribing declined during pregnancy. In Denmark, Norway and the UK, lamotrigine was the most commonly prescribed AED, whilst in the Italian regions, the older AEDs, such as sodium valproate, phenobarbital and carbamazepine were the most popular throughout the study period. The prescribing guidelines in all regions acknowledged the increased risks of some major congenital anomalies and neurodevelopmental problems associated with sodium valproate

exposure during pregnancy, and the increased risk of neural tube defects associated with carbamazepine. It was therefore unclear what was continuing to drive the higher use of carbamazepine and valproate in Italy. The Italian guidelines were the only ones that did not refer to an increased risk of congenital anomalies associated with phenobarbital and Italy was the only country where phenobarbital was commonly prescribed. The prescribing guidelines in all regions recommended that women prescribed AEDs were co-prescribed folic acid in advance of becoming pregnant and in the majority of regions this was for high dose folic acid (>0.5mg). Despite these recommendations, we found no evidence that co-prescribing of folic acid was usual practice during the pre-conception period.

The regional differences identified in AED prescribing patterns suggest different use, knowledge and/or interpretation of the scientific evidence base, and are unlikely to reflect informed choice of women. Increased efforts are needed to increase awareness of the potential risks associated with some of the older AEDs and particularly sodium valproate. More needs to be done to better inform clinicians and women of childbearing age taking AEDs of the need to plan their pregnancy and seek and receive complete preconception care. Preconception care is increasingly being recommended and organised for women with epilepsy, while the situation regarding psychiatric care and other indications is less clear.

**For medicines used to treat asthma**, regional differences were identified in the prevalence of prescribing of asthma medicines during and surrounding pregnancy. Regional differences were also identified in the extent to which different classes of asthma medicines were prescribed and the products most commonly



**Figure 3.8:** Prevalence of selective serotonin reuptake inhibitor (SSRI) prescribing in women with a delivery, between 2004 and 2010, during each of the 3-month time periods of interest

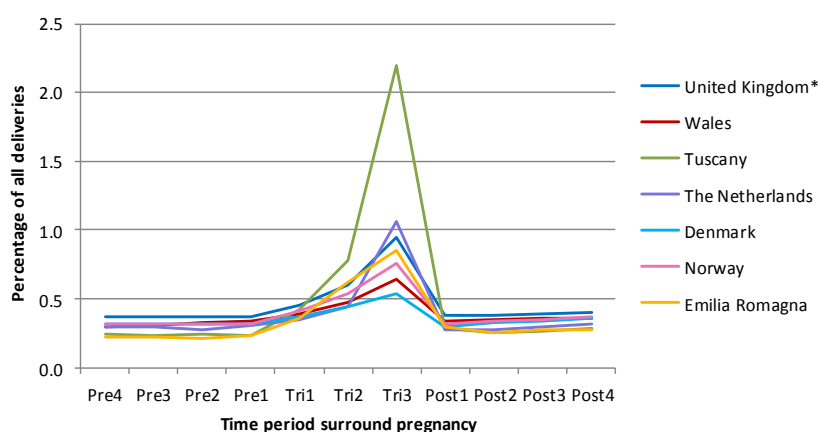
prescribed. In the UK, 90% of women who received a prescription for an asthma medicine during pregnancy received a prescription for a short-acting beta-2-agonist, compared with only 26% in the Italian regions. In Italy, however, 85-90% of women with an asthma medicine prescription received an inhaled corticosteroid, largely beclomethasone, compared with 50% in Norway and 60% in the UK and Denmark. Norway was the only region where the prevalence of ICS prescribing in a fixed-dose combination with a LABA was higher than the prescribing of ICS products not in a fixed-dose combination. During pregnancy, in all regions except the UK, the prescribing of long-acting beta-2-agonists declined during pregnancy, which may indicate that clinicians and pregnant women worry about using these relatively new inhaled medicines during pregnancy and the lack of information available on their safety.

In all regions, the prescribing guidelines advised that treatment for asthma during pregnancy should generally be the same as that for non-pregnant groups of patients. There was general agreement that SABAs were not teratogenic, with salbutamol and terbutaline being the recommended first choice. Budesonide is the ICS with the highest safety profile, however, Norway and Italy were the only countries where budesonide was recommended as the ICS of choice and Denmark was the only region where this was the ICS most commonly prescribed. Only the UK guidelines advised that when LABAs were required they should be used with an ICS and ideally as part of a fixed-dose combination product.

**For medicines used to treat diabetes**, regional variations were identified in the prevalence of prescribing for pregestational diabetes, which likely reflects regional differences in the prevalence of diabetes. During the second half of pregnancy, the prescribing of insulins increased in all regions, however large differences were observed in the extent of the increase, reflecting different prevalences of pharmacologically treated gestational diabetes (**Figure 3.9**). These differences are likely to reflect the fact that these European populations are at different risk for developing gestational diabetes, there is no European consensus on screening policies for gestational diabetes screening and that there are regional/national differences in the policies on and attitudes towards the treatment of gestational diabetes. Oral antidiabetic medicines largely consisted of metformin in all regions and in general were mainly prescribed during the year before pregnancy, followed by much lower levels of prescribing during the first and particularly the second and third trimesters. Future work is needed to explain the wide range of metformin prescribing patterns observed during the year before the start of pregnancy and to investigate the indications other than diabetes for which it is prescribed. During the later stages of the study period, increases in metformin prescribing during the second and third trimesters of pregnancy to treat gestational diabetes were observed in the Norwegian and two UK databases, however, in all other regions insulin continued to be the primary treatment for gestational diabetes throughout the study period.

### Use of electronic healthcare databases

In addition to providing information on the utilisation of medicines to pregnant women, this study has also demonstrated some of the strengths and limitations of electronic healthcare databases in Europe for evaluating medicine use and safety in pregnancy. As part of WP6 and the wider EUROMedicAT study, electronic healthcare databases have proven to be



**Figure 3.9:** Prevalence of insulin prescribing in women with a delivery, between 2004 and 2010, during each of the 3-month time periods of interest

a valuable source of information and beneficial for supplementing the data from congenital anomaly registries. Of particular note is the large number of pregnancies that are captured, the population-based nature of the data which provides a denominator population enabling the prevalence of prescribing to be calculated, and the fact that prescription data is recorded independently of the women, preventing the possibility of recall bias.

This study did, however, identify areas where data were lacking within some or all of the electronic healthcare databases and this reduced the scope of what could feasibly be evaluated using the data sources available. These limitations and restrictions in data availability highlighted areas where initiatives to collect and make available additional types of data could substantially enhance the utility of electronic healthcare databases for drug use and safety in pregnancy research, including their use for the evaluation of pregnancy prevention programmes. The key areas identified were

- Availability of data on pregnancies that end in a spontaneous or induced termination
- Availability of hospital, specialist and private prescribing and hospital pharmacy dispensing data
- Recording of the indication for prescribing
- Recording of data on maternal patient characteristics and lifestyle factors such as smoking, alcohol, body-mass-index and socioeconomic status
- Availability of data on contraception use and prescribing
- Availability of complete data on dose and DDD

### **3.7 WP7 Implications of the internet in relation to medication access and safety information**

#### **3.7.1 Work undertaken**

- Descriptive cross-sectional survey of E-pharmacies to compare and contrast medication safety information and purchasing procedures from bona fide and non bona fide e-pharmacy websites selling Isotretinoin and Mistroprostol (**Deliverable 30**)
  - Review of literature on Internet medication purchasing
  - Review of literature on the online availability and access to information for consumers on teratogenic effects of Isotretinoin
- A web-based survey to develop an understanding of pregnant woman's use of the Internet for medication safety information and purchase (**Deliverable 31**)
  - Review of literature on attitudes of women taking medications in pregnancy

#### **3.7.2 WP7 results and foreground**

The Internet has now become an important source of information and access to products. Research exploring the implications for drug safety and pharmacovigilance is relatively new but rapidly spreading. Work Package 7 (WP7) Implications of the Internet in Relation to Medication Access and Safety Information was a four phase, multi-method, scoping study conducted at Ulster University between in March 2011 and December 2013 as part of the EUROmedicat project. WP7 combined both quantitative and qualitative research methods to explore the behaviour of pregnant women in their use of the Internet for medication safety information and for medication purchase and develop recommendations for regulators in relation to the role of the Internet in drug safety.

### A brief summary of the key points from the literature

- Safety information available online was considerable and there was robust evidence of published and readily available data on the teratogenic effects of medications such as isotretinoin from regulated medicine agency sites, teratology information services and professional networks.
- The literature also indicated that women lacked knowledge about the potential risk of congenital anomalies (CA) from medication use in pregnancy
- Women perceived it was safer to take medication in trimester two and three
- some women were reluctant to take important prescribed medication because of fear of CA and misconceptions about safety.

### Evaluation of E-pharmacies (Deliverable 30)

The key term 'buy isotretinoin' was keyed into the five most common search engines and the first 10 sites were selected from each. The resultant 50 e-pharmacies were searched to obtain purchasing information on isotretinoin and were evaluated in terms of the 'general website' criteria, 'e-pharmacy criteria as well as Pregnancy Prevention Programme specific criteria'.

### Summary of main findings regarding online purchasing

- It was very easy to purchase prescription only medications without the requisite prescriptions
- All 7 samples received of 8 purchased from sites not requiring prescriptions were proven by laboratory analysis to be Isotretinoin
- None of 7 samples were received in a properly labelled container with an appropriate patient information leaflet
- One of 7 samples had a tiny 'Avoid in Pregnancy' symbol on the foil packet, the others no warning at all. All samples came from India.

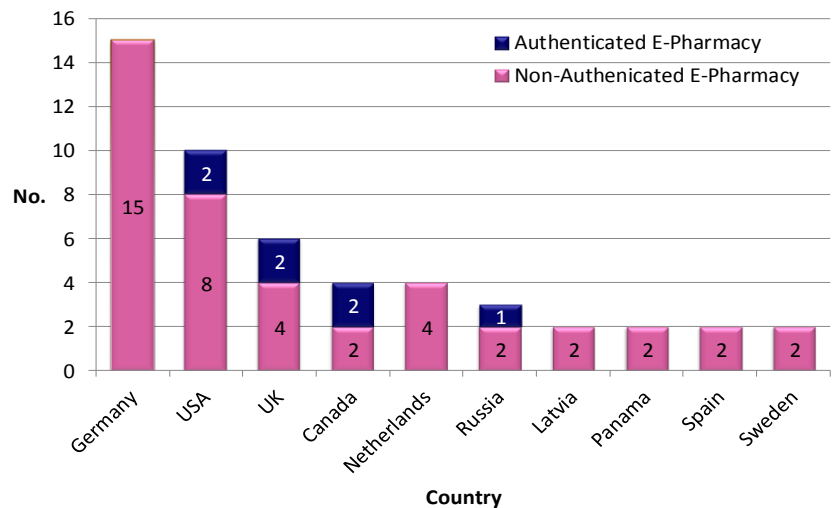


Figure 3.10: Location of E-pharmacies



**Figure 3.11:** Illustration of received isotretinoin sample

Conclusions from the study: Women of childbearing age have the opportunity to self-purchase medications directly from websites that do not provide any form of risk assessment, pregnancy prevention advice, or adequate warnings of the dangers associated with taking these medications, nor require a prescription.

The majority of the few sites that required a prescription were prepared to accept a fax or email which is in contravention of the recommendations of the Royal Pharmaceutical Society of Great Britain about what constitutes a valid prescription. None of the purchased medicines were packaged according to the European Council Directive 2001/83/EC. Females obtaining Isotretinoin or Cytotec from non bona-fida pharmacy sites may be at risk of becoming pregnant and being exposed to known and unknown potential teratogens.

### **Web-based survey (Deliverable 31)**

A web-based survey was undertaken to develop an understanding of pregnant woman's use of the Internet for medication safety information and purchase. The survey Instrument was developed, adapted and piloted (items from previously validated instruments by Närhi et al 2008; Peterson-Clarke et al 2010; and Lagan et al 2011) and ethical approval was obtained from Ulster University Institute of Nursing and Health Research Ethics Filter Committee. Participants had to 18 years of age or over, currently pregnant or had a baby in the last year, living in the UK and able to understand English. The age distribution was 18-45 (mean 30), 244 women were from England, 21 from Wales, 10 from Scotland and 9 from N. Ireland. A significant proportion held higher degrees (44% n=125). However, it is important to note, *this sample should not be* considered representative of the population, but may be considered a wide cross section of women using the Internet.



### Summary of main findings

Overall, 111 (39.1%) of the study participants were taking at least one medication that was not a mineral or vitamin when they became pregnant and this included: antibiotics, inhalers, anti-depressants, antiepileptics and diabetes medication. The sample selected included women who did not have a chronic condition requiring medication prior to becoming pregnant (60.2% n=171). Chronic conditions suffered by women included asthma, depression, diabetes and epilepsy. Women were asked if they were prescribed medication would they change their medication when planning a pregnancy and 17% (n= 47) said "yes",

38% (n=109) “yes” when the pregnancy was confirmed and a small proportion would not change medication in either circumstance (15% n=43).

#### *Women’s willingness to take any medication during pregnancy*

The majority of women in the study were not happy taking any medication during pregnancy (60% n= 169).

#### *Use of the Internet for Medication Safety information in Pregnancy*

The majority of women used the Internet to search for information about medication safety in pregnancy (76% n=217) and health service sites were the most used online source (92.6% n=201) followed by social media (85% n=185 ) and pharmacy/drug companies (53% n=115). The majority said the information either verified or reassured them it was ‘ok’ to take the medication or influenced their decision not to take the medication. Trustworthiness of sites was an important factor and the majority of women trusted safety information obtained from health service sites (84%). It was surprising to note that 71% (n=180) women had never seen these pregnancy warning symbols.

**The online focus groups** were conducted with two groups of women (n=11 and n= 5) using asynchronous messaging to explore online purchasing activities and to seek a deeper understanding of their information seeking behaviour identified. The majority of participants portrayed a similar pattern of behaviour with regard to searching the Internet, i.e. entering a question or the name of the medication into a search engine. The reasons given for accessing information online were ‘convenience’ ‘accessibility’ and ‘cost savings’. Generally speaking, the participants mentioned they would trust information they accessed online if it was from a ‘reputable source’ such as the National Health Service (NHS) in the UK. Women were aware of the need to be cautious about the source of the information retrieved:

*“...you can never be 100% sure that the medication you are getting is what you have ordered or where it is coming from”*

*“You don’t know if it is safe”*

*“May be the wrong medication for you or your illness, something more serious may be missed”*

Many demonstrated the benefits of having the availability of the Internet as an information source:

*“...you can purchase medications at a cheaper cost than from retailers”*

*“ ... the easiness of it being delivered to your door*

*“... cheaper and can get a lot of things online **without prescription** and get things that you can’t get in the UK”*

Those who actually purchased medications were concerned about the ‘quality of the medication’ they purchased from the Internet and stated they read the testimonials and blogs provided by customer reviews:

*“I read reviews from other apparent customers”*

*“I did lots of research about the site from customer’s reviews doing a Google search”*

Others demonstrated expertise and entrepreneurial skills:

*“it was just a google search... I looked at a lot of pharmacy websites and also Amazon. In the end I actually purchased from someone on eBay that showed an actual photo of the product they had rather than a stock photo. I also spoke with the seller and got some background info on why they were selling etc. Buying this way saved me £30 off the retail price!!”*

*“ I did a google search and checked out the top5 sites listed and read reviews in each site about the service. I was wary of buying medication on the Internet, it was my first time but I thought if I had a*

*bad experience, I wouldn't bother again but the site I used first time has been good and I am a recurring customer a year on..."*

Conclusions from the study: Data from the online purchasing experiment with 50-e-pharmacies demonstrated that it was easy to purchase pure compounds without prescription. The web-based survey indicated that women were using the Internet selectively to either find or verify information to enable them to inform their decisions. Women were savvy about the quality of sites accessed and 217/284 accessed bona fide health service sites. The online focus groups substantiated the data from the literature about accessibility, affordability, convenience and the need to check medication safety information online.

### **3.8 WP8 Dissemination workshop**

#### **3.8.1 Work undertaken**

- Dissemination workshop (Deliverable 32)
- Recommendations for pharmacovigilance for drug safety in pregnancy (Deliverable 33)

#### **3.8.2 WP8 results and foreground**

The main objective of WP8 was to organise the EUROmediCAT dissemination workshop. WP8 was also responsible for drafting recommendations for pharmacovigilance for drug safety in pregnancy. WP8 supplemented the scientific dissemination being undertaken in other workpackages and co-ordinated by WP1 and took charge of organising a final dissemination workshop and creating national dissemination plans.

EUROmediCAT workshop "Safety of medication use in pregnancy"

The final workshop European Conference "Safety of Medication Use in Pregnancy" was organized in Poznan February 2-4, 2015. Recommendations and further dissemination strategy was agreed. In order to reach the widest range of possible stakeholders with the information of the planned conference a total of 2000 leaflets, 300 invitations and 45 posters have been send to more than 1100 Polish wards, 140 national and regional Polish consultants, 95 Polish departments and clinics, 50 patients societies and association of physicians, EUROmediCAT partners and subcontractors, a total of 1000 emails with conference communique were sent to Polish Universities, hospitals, health care professionals, statement of the conference was published on many websites and in Polish journal "Prenatal Cardiology". Europe and worldwide dissemination was conducted via mailing lists and newsletters relevant to reproductive pharmacovigilance. The conference website: [www.euromedicatconference2015.eu](http://www.euromedicatconference2015.eu).

The conference was very well attended, with 620 participants registered from 24 countries. Among the invited speakers, panel members and chairs were experts in the field of pharmacoepidemiology, teratology, genetics, gynecology, neurology and psychiatry. The Conference was held under the patronage of Polish Minister of Health Bartosz Arłukowicz, Polish Chairman of the Polish Parliamentary Health Committee Tomasz Latos, Marshal of Wielkopolska Province Marek Woźniak, Mayor of the City of Poznań Jacek Jaśkowiak, and Rector of the Poznan University of Medical Sciences Prof. Jacek Wysocki.

During the first day of the Conference there was a Satellite Conference "Prevention of congenital malformations - pregnant women therapy safe for the fetus" in Polish, addressed to Polish health care professionals, medical, midwifery and nursing students, giving the opportunity to educate and raise awareness among clinicians and policymakers in Poland regarding medication safety in pregnancy,

congenital anomaly prevention, and the important work of the Polish Registry of Congenital Malformations as a part of EUROCAT. Polish participants were presented lectures concerning inter alia recommendations for treatment of pregnant women with diabetes, epilepsy and asthma, and proceedings in pregnant women with ovarian tumors and with breast cancer.

Fifty abstracts for poster presentation were submitted. Thirty three of the abstracts were selected for poster session of “Safety of Medication Use in Pregnancy” Conference (classified in seven categories: epilepsy, mental health, depression, asthma, prevention and public health, natural and herbal products, methodology, other) and thirteen for Satellite Conference. Twenty four posters and eighteen oral presentation abstracts from the Conference will be published in the journal “Pharmacoepidemiology and Drug Safety”.

All EUROmediCAT workpackages results were presented during the Conference in each of the session. After the session the panel discussion were held, giving the opportunity to discuss the results with all the key stakeholders from across Europe and regional stakeholders from Poland. Session 7 “Recommendations for reproductive pharmacovigilance in Europe” of the Conference was specifically devoted to Recommendations for reproductive pharmacovigilance in Europe (**Deliverable 33**).

Sustainability in terms of the continuation and development of the EUROmediCAT system was considered. Conference organizers received a letter from the Member of the European Parliament Boleslaw Piecha, in which he stressed the importance of research undertaken by EUROmediCAT and offered assistance in organizing a similar conference in the forum of the European Parliament. It is assumed to take action in order to organize such a conference in the near future.

Attention shall be given on the fact that in the Conference participated representatives of patient organizations and people born with physical and visual impairments as a consequence of thalidomide use by their mothers during pregnancy. One of invited speakers was Geoff Adams-Spink, Trustee of the Disability Rights in United Kingdom and Chairman of the European Dysmelia Reference Information Centre. During the Conference representatives of patient organizations and other patients, took part in the meeting with Geoff Adams-Spink and medical geneticist. The meeting gave the opportunity for patients to exchange experiences and got help and advice from people involved in the fight for real improvement in people's quality of life and helping them to retain independence and dignity. The Conference was the occasion for a press, radio and TV release in Poland.

PUMS stimulated the other partners to widen the scope of their dissemination activities and helped WP1 to collect together information about dissemination by all partners. The Polish National Dissemination Plan has been developed and implemented. The plan assumed education and dissemination of knowledge about EUROmediCAT, European Conference and recommendation agreed during the Conference, through four groups of people: students, healthcare professionals (e.g. physicians, midwives and nurses), policy makers and the general public. The Polish National Dissemination Plan was fully implemented.

**Scientific publications relating to the foreground of EUROmediCAT (Table 6.1) and dissemination activities (lectures, workshops, conference lectures, leaflets, Bachelor's dissertation, recruitment of EUROmediCAT volunteers, interviews, website, newsletters, posters, presentations, articles, publications, article in press, brochure on EU projects, letters to politicians) took place (Table 6.2). A new website in Polish ([mamapodopieka.pl](http://mamapodopieka.pl)) dedicated to the project has been designed. It provides**

information on the project, maternal diseases and medication during pregnancy. It is planned to update and supplement information on this website, even after the end of the EUROmediCAT project.

### **EUROmediCAT Recommendations: European Pharmacovigilance concerning Safety of Medication Use in Pregnancy**

The Recommendations for European and national medicines regulatory agencies, public health authorities and professional clinical bodies are

To improve future pharmacovigilance

To inform future drug safety measures

The recommendations are designed to help make better use of current data, networks and infrastructures in Europe, to achieve a more integrated system and better dissemination of knowledge and to raise the level of reproductive pharmacovigilance to meet women's reasonable expectations.

These recommendations concentrate particularly on safety in early pregnancy in relation to the risk of congenital anomalies. Wider perspectives should also be taken with respect to other adverse pregnancy outcomes (such as miscarriages, preterm birth or intrauterine growth retardation) and particularly neurobehavioural effects of medication exposure in pregnancy, with respect to the effects of the diseases/conditions themselves on pregnancy outcome, with respect to herbal medications, and with respect to the period of lactation, but these are not the specific focus of these recommendations.

Near the end of the EUROmediCAT project in January, 2015, all EUROmediCAT Workpackage Leaders were asked to contribute recommendations arising from their workpackage. A draft set of the full project recommendations was circulated to the EUROmediCAT Steering Group for comment and approval. The second draft of recommendations was presented for discussion at the final EUROmediCAT conference in Poznan February 2-4. All External Chairs and Panel Members were invited to endorse the recommendations (still in progress at time of drafting of this Report) before scientific journal and website publication.

The 27 Recommendations were grouped under three subheadings as follows

General Regulatory and Public Health Considerations (9)

Improving Safety of use of antidiabetics, antiepileptics, antidepressant, antiasthmatics (7)

Methodology and Infrastructure for Reproductive Pharmacovigilance (11)

**Members of the EUROmediCAT Steering Group and EUROCAT registries have offered to translate the Recommendations into national languages, and will send the Recommendations to their national medicines regulatory authorities and public health authorities. As WHO Collaborating Centre for Surveillance of Congenital Anomalies, the Centre for Maternal, Fetal and Infant Research at Ulster University (Co-ordinator of EUROmediCAT) will seek to engage the WHO with regard to the Recommendations (Deliverable 33).**

## 4. Potential impact, main dissemination activities and exploitation of results

### 4.1 Overview of potential impact for different stakeholders

EUROmediCAT will influence different stakeholders in relation to medication use in pregnant women. A number of potential impacts were considered:

- Healthcare professionals
  - A better understanding of the benefit-risk profile of providing pregnant women with antiasthmatics, antiepileptics, insulin analogues and SSRIs for improved evidence-based decision making
- Policy makers
  - A set of recommendations for promoting the safe use of teratogenic medication and promoting the investigation of teratogenicity of medication
  - Awareness of the impact of data protection legislation on the conduct of scientific research
  - Awareness of the impact of the internet on medication use in pregnancy and drug safety management programs
- Pregnant women
  - Improved informed decision making in relation to the teratogenic risks of anti-asthmatic, antiepileptic, insulin analogue and SSRI medication use
- Research community
  - Access to fully documented, standardised, validated pharmacovigilance databases for evaluating safety of medication use in pregnancy in relation to the risk of congenital anomalies
  - Access to newly developed EUROmediCAT software for pharmacovigilance research relating to pregnancy
  - Access to EUROmediCAT website tables showing the frequency of medication exposures in pregnant women
  - Set of recommendations in relation to investigating teratogenic risk of medication

### 4.2 Impact of central database and software development

A fully documented, standardised, validated pharmacovigilance database was created under WP2. This database enables evaluation of the safety of medication use in pregnancy in relation to the risk of congenital anomalies. This database currently covering over 7 million births in 15 European registries 1995-2012 is unique in the world due to its size and population coverage. Analysis based on this database will add significantly to the literature as few databases have sufficient statistical power to identify associations between rare anomalies and rare drug exposures. Strengths of the database include information on both exposed and unexposed pregnancies, inclusion of TOPFA, and mainly prospectively recorded medication exposure information. Limitations include little information on dose, underascertainment of medication exposure depending on maternal disease/ health condition, and the lack of non-malformed controls.

The development of a routine pharmacovigilance system for the detection of possible new teratogens relating to first trimester medication exposure in a timely manner makes an important contribution to pharmacovigilance as it offers a viable alternative to expensive cohort studies or less reliable spontaneous reporting of adverse reactions. These data are already routinely collected and the automated process should improve the efficacy and cost effectiveness of conducting pharmacovigilance in relation to pregnancy. Furthermore, the fact that we were able to identify known associations, such as the spina bifida and valproic acid association, strengthens the validity and reliability of using this database for pharmacovigilance research.

The development of the EUROmediCAT website-accessible tables showing the frequency of medication exposures in for congenital anomaly cases in the database increases efficiency of study feasibility assessment and protocol development in future.

The development of software and protocols for prescription data linkage and cohort linkage will facilitate such research in the future.

### 4.3 Impact of prescription data linkage

The linkage of prescription databases to congenital anomaly registers improved the information on medication use in pregnancy, in particular for medication that is not very well recorded in medical files, such as medication for use when necessary and medication for short time use.

Our experience with the prescription data linkage has resulted in the following recommendations on prescription data linkage (see also **Deliverable 13**). These recommendations are included in the overall recommendations for pharmacovigilance for drug safety in pregnancy (**Deliverable 33**).

#### Recommendations on prescription data linkage

A sufficient sample size is one of the main requirements for a high quality case-control study. Combining several databases with uniform data definitions, on outcome and exposure, is an efficient way to obtain a large sample size. However, due to national governance and data protection regulations regarding the administrative (prescription) databases, the linked datasets could not be combined into one large central dataset. Health authorities should reconsider regulations that limit the use of electronic health care database with information on prescription medication databases in large scale international collaborative projects. As a consequence of the difficulties encountered during the data linkage process, EUROCAT has co-signed a statement from non-commercial organisations on protecting health and scientific research in the data protection regulation.<sup>2</sup> To gain knowledge on safety of medication use in pregnancy, valuable data sources already exist. Combining these data sources between countries (pooled databases) is the key method to obtain timely and continuing information on possible risks associated with medication use in pregnancy. In addition, these electronic health care databases should allow linkage to all women giving birth, and women who choose to terminate their pregnancy for fetal anomalies or suffer foetal losses.

We recommend the use of tailor made exposure definitions in studies on medication use and congenital anomalies, depending on the medication and congenital anomaly that are subjects of the study. The use of prescription data allows for diverse exposure definitions, including repeat prescriptions and the use of broad and strict exposure periods.

To improve the use of prescription data, information on amount prescribed and daily dose -preferably in a standardized way such as DDDs, information on indication, information on medications prescribed in hospital and in private practice should be included in the administrative databases.

### 4.4 Impact of drug safety studies

Given the rarity of congenital anomalies and ethical considerations, it is unlikely that clinical trials will ever be undertaken in this area, increasing the potential impact of our work.

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[http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy\\_communications/documents/web\\_document/WTP055584.pdf](http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/WTP055584.pdf)

### **Asthma medications**

Although our study confirmed a small increased risk for cleft palate and gastroschisis after exposure to inhaled beta-2-agonists and for anal atresia after exposure to inhaled corticosteroids in the beginning of the pregnancy, it is important that pregnant women with asthma continue their medication during pregnancy. Use of prophylactic inhaled steroids, where we did not find increased congenital anomaly risk, seems to be the best solution for the treatment of maternal asthma in pregnancy to prevent the harmful effects of asthma exacerbations and to reduce the need for high dose inhaled beta-2 agonists or systemic medications where we find evidence of teratogenic effects. This is important new evidence for use by clinicians and women. For the health of both the mother and the fetus, it is important that health services help women with asthma to achieve good control prior to conception and during pregnancy.

### **New anti-epileptic drugs**

We did not find an increased risk of orofacial clefts (OCs) after Topiramate monotherapy, but we found an increased risk of cleft lip with or without cleft palate (CL/P) after exposure of Topiramate polytherapy. The data should be interpreted with caution because of the low numbers. Women with epilepsy have to continue their medication also during pregnancy. The potential risks should be balanced against the risk as well as the comparative effectiveness of other antiepileptic drugs, among others valproic acid with much higher CA risks. Future studies with more exposed pregnancies to new AEDs are needed.

### **Insulin analogues**

Our data show that women exposed to insulin analogues during the first trimester of pregnancy have a decreased risk of congenital anomalies especially congenital heart defects (CHD) compared with the use of human insulin. But the proportion of still-birth and spontaneous abortion is higher among the only insulin analogues group compared to only human insulin group. This needs further investigation. Based on our data, women who use insulin analogues can safely continue their medication when becoming pregnant.

### **SSRIs**

The complexity of balancing the potential harms and benefits of SSRI use in pregnancy necessitates that healthcare providers review the delivery of specialist preconception care for women with depression, and organisation of services to meet the need for alternative non-pharmaceutical therapies where appropriate and without delay for women in need. Health authorities in each country should review the appropriateness of use of SSRIs by women of childbearing age and pregnant women in their populations, and design care pathways starting in the preconception period for medicines management, and continuing also during pregnancy to support and potentially offer enhanced ultrasound scan monitoring for congenital anomalies (prenatal detection of severe CHD will, even late in pregnancy, allow referral for birth at a hospital with neonatal cardiology service), and to appropriate neonatal care for both mother and baby.

### **Reproductive pharmacovigilance methodology**

We have shown that there are a number of previously unexploited opportunities to provide evidence regarding safety of medication use in pregnancy. Their use and potential improvement (particularly in regard to data on dose and on indication for medication) are part of the EUROmedICAT Recommendations (**Deliverable 33**). We have shown that a network of congenital anomaly registries can work together successfully for pharmacovigilance in Europe, but note that there are at present no funding opportunities to continue this valuable work.

## 4.5 Impact of drug utilisation studies

EUROmediCAT drug utilisation studies demonstrated that a large number of pregnant women receive medicines to treat chronic conditions and there is a need for more resources and emphasis to be put towards preconception care and counselling. We also demonstrated large regional and national differences in medication exposures during pregnancy. These differences may be explained by differences in the prevalence/incidence of the chronic maternal diseases or differences in level of/choice of treatment as suggested by the variation found in prescribing guidelines. Such comparative data are very useful for health authorities. We have demonstrated that there is different interpretation of the scientific evidence base in different countries, and more needs to be done to raise awareness of the potential risks known to be associated with some medicines, particularly sodium valproate, to ensure appropriate prescribing.

The protocols developed for these studies and the much greater understanding of the healthcare databases accessed will facilitate drug utilisation studies in future in many other medication areas where this is needed (e.g. for thyroid diseases, rheumatoid arthritis and autoimmune diseases, hypertensive conditions).

## 4.6 Dissemination activities

A wide range of dissemination activities were employed during the lifetime of the EUROmediCAT project including a EUROmediCAT article in Projects Magazine, a EUROmediCAT conference, EUROmediCAT flyers, interviews, the lay press, newsletters, oral presentations at scientific and non-scientific events, scientific papers and abstracts, web news items/pages (**Table 6.1a, 6.1b and 6.2**). A national Polish dissemination plan was written under WP8 and a communication plan was developed under WP1. The plan identified a number of different target groups for dissemination of the EUROmediCAT project:

1. EUROmediCAT
  - EUROmediCAT Project partners
  - EUROmediCAT subcontractors
2. Policy makers & regulators
  - regulators (national / international)
  - (National) government and EU policy makers
  - Public health officials
  - European Medicines Authority (EMA)
  - Groups concerned with quality of internet sites
3. Scientific community
  - Academic researchers
  - Academic associations (ISPE, ISoP, ENTIS)
  - CA registry staff
4. Individuals and associations involved in the treatment and prescription of medication to all (pregnant) women and in particular women with epilepsy, diabetes, depression and asthma
  - Healthcare professionals (medical clinicians, midwives, nurses, health visitors, pharmacists)
    - In particular healthcare professionals involved in the care of women with asthma, mental illness, diabetes and epilepsy.
  - Professional associations
  - Teratology information services (giving advice to clinicians)
  - EUROmediCAT advisory board: clinical representatives
  - Medical, nursing, midwifery and all healthcare students
5. Pregnant women & women planning a pregnancy but in particular women with epilepsy, diabetes, depression and asthma
  - Patient support groups
  - Women's / mothers groups
  - EUROmediCAT advisory board: patient representatives

- o High school students
6. Pharmaceutical companies

### 4.6.1 Dissemination material

**EUROmediCAT website:** A EUROmediCAT website (<http://euromedicat.eu/>) was created following initiation of the EUROmediCAT project. The purpose of the EUROmediCAT website is to disseminate EUROmediCAT project output, increase awareness of EUROmediCAT and to facilitate cooperation and exchange of documents for EUROmediCAT participants via the “members only” webpages. The EUROmediCAT website will continue to be maintained following completion of the EUROmediCAT project.

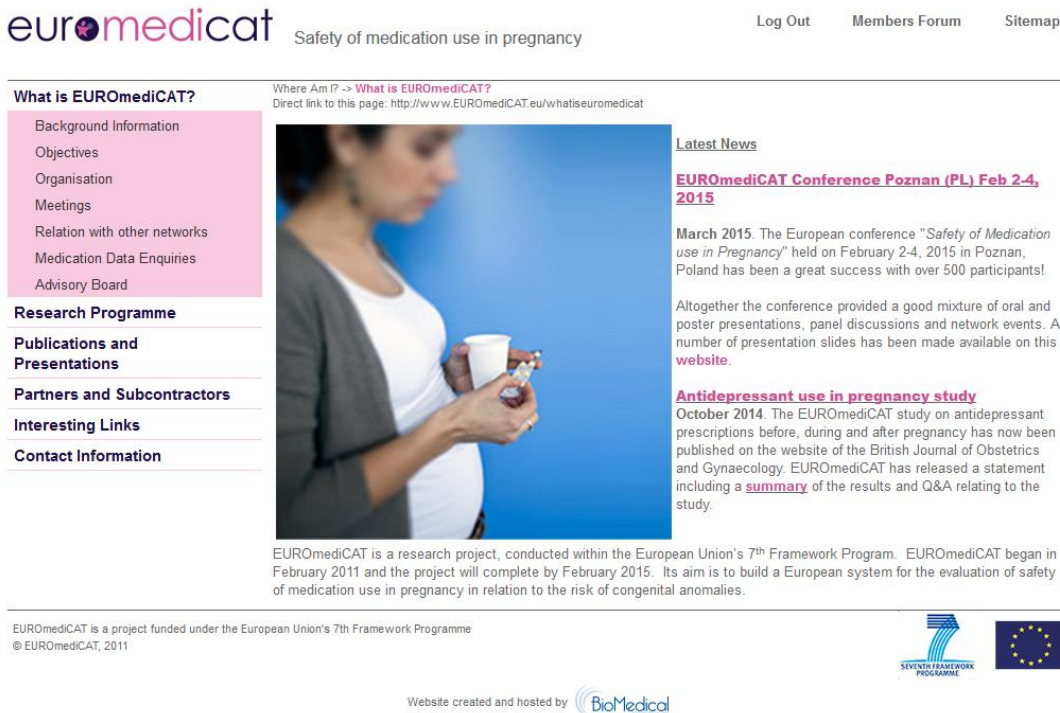


Figure 4.1: EUROmediCAT Website 20 April 2015.

**EUROmediCAT leaflet (2011):** A EUROmediCAT leaflet was designed late 2011 in the initial stages in the project in order to be distributed at scientific and non-scientific events by visiting EUROmediCAT participants. This leaflet is also available from the EUROmediCAT website.

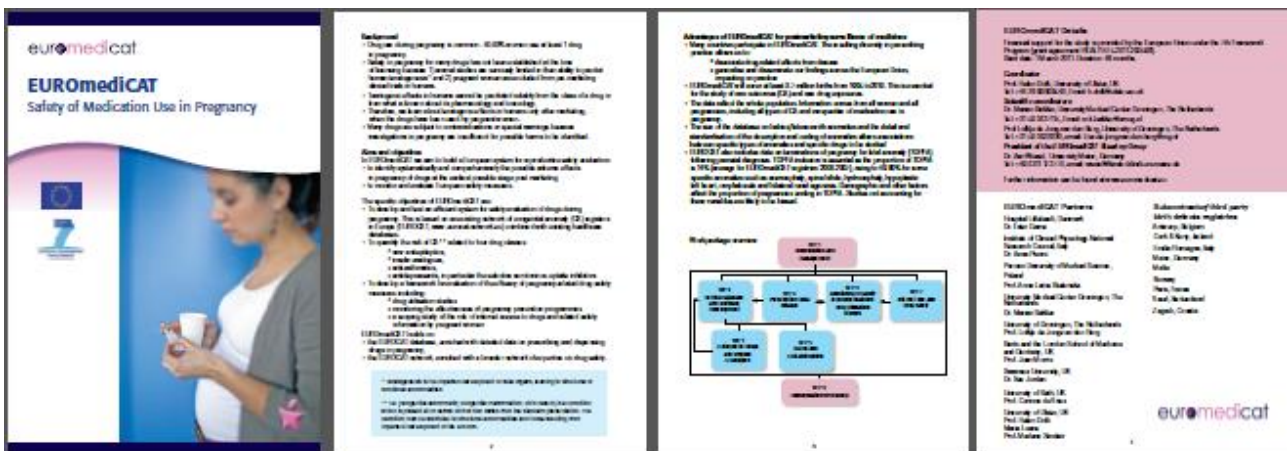


Figure 4.2: EUROmediCAT flyer 2011.

**EUROmediCAT conference website:** A EUROmediCAT conference website (<http://euromedicatconference2015.eu/>) was created late 2014 in order to increase awareness of the EUROmediCAT conference and aid dissemination of the EUROmediCAT conference outputs.

**EUROmediCAT leaflet (2015):** A EUROmediCAT leaflet was designed in 2015 in order to be distributed at scientific and non-scientific events by visiting EUROmediCAT participants. This leaflet is also available from the EUROmediCAT website.

The leaflet is titled "Projects" and "EUROmediCAT Special Edition". The main headline is "Drug safety during pregnancy". Below the headline, it says "EUROmediCAT - building a European system for the reproductive safety evaluation of medicines". The leaflet contains several sections of text, including an introduction to the project, a list of speakers, and a call to action for the conference. The text is arranged in columns and includes various sub-headings and bullet points.

Figure 4.3: EUROmediCAT leaflet (2015)

The website has a header with the title "Safety of Medication Use in Pregnancy" and the euromedicat logo. Below the header, there is a navigation menu with items like "Home Page", "Photo Gallery", "General Information", "Honorary Patronage", "Conference Committees", "View our speakers", "Scientific Program", "Abstracts", "Fee", "Accommodation", "About Poznan", "How to get to Poznan", "Participant's Panel", "Amber Passion", "Simone Mangos", and "Contact". The main content area includes a "Photo album" with three images, a "Welcome Message" section, and a "OUR SPEAKERS" section featuring a portrait of Lotjke T. W. de Jong van den Berg. The footer contains logos for euromedicat, the Polish Ministry of Health, and the European Union.

Figure 4.4: EUROmediCAT Conference website 20 April 2015

## 4.7 Exploitation of results

Our project concerns pharmacovigilance, which by its nature is a continuous activity, as new drugs come on the market and prescribing and medication use changes. Our aim was to **“to build a system for reproductive safety evaluation, to enable the systematic and comprehensive identification of possible adverse effects in pregnancy of medication in humans at the earliest stage post marketing and to enable the monitoring and evaluation of safety measures taken in Europe”**

We have achieved what we set out to do over the last four years, and now it is important to use this system for future pharmacovigilance and to radically change the situation regarding the lack of available medication safety information for pregnancy.

The EUROmedICAT Steering Group will continue to convene after the completion of the EUROmedICAT project. During the last steering group meeting in Poznan, February 4<sup>th</sup>, 2015, a number of items were agreed upon in order to facilitate continued effort:

1. A post-FP7 EUROmedICAT agreement was agreed upon by all members of the EUROmedICAT steering group. This document outlines i) governance of shared data arising from the FP7 project EUROmedICAT, ii) the infrastructure and communication network for future funding proposals and projects, iii) agreements between partners for future grant proposals and iv) established a basis for updating and maintaining the EUROmedICAT database.
2. New terms of use for the EUROmedICAT central database and a system level security policy were agreed upon in order to ensure continued access to the EUROmedICAT central database and to ensure that appropriate data protection measures and processes are in place. Issues such as authorship of scientific papers generated by EUROmedICAT central database data, system audit, system protection as responsible persons were identified.
3. A EUROmedICAT data and procedures document was agreed upon in order to ensure standard data processing and data quality.

Other indications of continuing commitment to improving data quality and availability:

- Continuing linkage between CA registries and prescription data in the two Italian centres, including improving the linkage rate
- Design of a new medication exposure recording form in Poland
- Addition of a number of other EUROCAT registries to the EUROmedICAT network
- Interest from several further EUROCAT registries in conducting linkage to prescription data

During the EUROmedICAT Project, we began collaboration with the Uppsala Monitoring Centre as part of Workpackage 2 on Signal Detection, and the intention is to grow this collaboration in order to evaluate signal detection relating to congenital anomalies which is based on spontaneous reports worldwide.

After the Poznan Conference, the EUROmedICAT Steering Group met with members of ENTIS (European Network of Teratogen Information Systems) in order to discuss joint advocacy work regarding pharmacovigilance, and exchange of signals and possible joint projects in future. These initiatives will be further discussed by the Steering groups of both networks.

EUROmedICAT is registered on the EncePP Register of research, and EUROCAT registries are registered in the database of resources. Representatives participate in the EncePP network of European Centres for Pharmacovigilance and Pharmacoepidemiology. An updated entry in the registers will reflect the work done over the last four years in building data resources.

We also continue to work with and grow collaboration with civil society organisations. The European Women's Health Institute was represented on the EUROmediCAT Advisory Board. The International Diabetes Federation, International Epilepsy Bureau, Disability Rights UK/European Dysmelia Reference (EDRIC) and the Rare Diseases umbrella organisation EURORDIS were invited to the EUROmediCAT Conference in Poznan as Panel Members and have expressed an interest in continuing collaboration. They are being asked to endorse and advise on the dissemination of the EUROmediCAT Recommendations: European Pharmacovigilance concerning Safety of Medication Use in Pregnancy (see Workpackage 8 above). A new Advisory Board for the future will also be considered.

The Poznan Conference organizers (Poznan University of Medical Sciences) received a letter from the Member of the European Parliament Boleslaw Piecha, in which he stressed the importance of research undertaken by EUROmediCAT and offered assistance in organizing a conference in the forum of the European Parliament. It is assumed to take action in order to organize such a conference in the near future.

Two main problems threaten the sustainability of the EUROmediCAT network and its research:

- The new European Data Protection regulations which are under negotiation, unless suitable exemptions are agreed, may prevent use of data without consent and sharing across borders, which is absolutely essential in this area. We believe the Public Good in this area far outweighs any risks to the individual, and that the public themselves would want their data used in this way. EUROmediCAT has joined with EUROCAT in putting forward its case, and has supported the Wellcome initiative regarding Data Protection.
- The lack of any provision for medication safety research in the Horizon2020 programme will make it difficult to find sufficient funding to sustain the network and to retain highly experienced staff.

The first EUROmediCAT Recommendation is as follows:

**“The scarcity of information on medication safety in pregnancy, in relation to risk of congenital anomaly but also neurobehavioural and other effects, is unacceptable and must be remedied by more investment in research and pharmacovigilance. A mechanism whereby pharmaceutical companies contribute to an independent pharmacovigilance and research funding pot with ring-fenced use for pregnancy and lactation is urgently needed. This would both monitor new medicines and remedy the deficit of information on medicines in common use.”**










## 5. Public website address and relevant contact details

EUROmediCAT website: <http://www.euromedicat.eu/>

EUROmediCAT Polish website: [mamapodopieka.pl](http://mamapodopieka.pl)

EUROmediCAT conference website: <http://euromedicatconference2015.eu/>

**Table 5.1a:** EUROmediCAT Steering Group members from partner institutions

Beneficiary name	Steering group members	Country	Logo
Hospital Lillebaelt	<a href="#">Dr Ester Garne</a>	Denmark	
Institute of Clinical Physiology-National Research Council	<a href="#">Dr Anna Pierini</a>	Italy	
Poznan University of Medical Sciences	<a href="#">Prof Anna Latos-Bielenska</a>	Poland	
Queen Mary, University of London	<a href="#">Prof Joan Morris</a>	UK, England	
Rijksuniversiteit Groningen	<a href="#">Prof Lolkje de Jong-van den Berg</a>	Netherlands	
Swansea University	<a href="#">Dr Sue Jordan</a>	UK, Wales	
Ulster University (Coordinator)	<a href="#">Prof Helen Dolk</a> <a href="#">Dr Maria Loane</a> <a href="#">Dr Johannes Michiel Luteijn</a>	UK, Northern Ireland	
University of Bath	<a href="#">Dr Rachel Charlton</a> <a href="#">Prof Corinne de Vries</a>	UK, England	
University Medical Centre Groningen	<a href="#">Dr Marian Bakker</a>	Netherlands	

**Table 5.1b:** EUROmediCAT Steering Group members from non-partner institutions

Affiliation	Steering group members	Country
University of Bergen	<a href="#">Prof Kari Klungsoyr</a>	Norway
University of Mainz	<a href="#">Dr Awi Wiesel</a>	Germany

**Table 5.2:** List of work package leaders

Work Package	Work Package Leader
1	<a href="#">Prof Helen Dolk</a>
2	<a href="#">Dr Maria Loane</a>
3	<a href="#">Dr Marian Bakker</a>
4	<a href="#">Prof Lolkje de Jong-van den Berg</a>
5	<a href="#">Dr Ester Garne</a>
6	<a href="#">Dr Rachel Charlton</a>
7	<a href="#">Prof Marlene Sinclair</a>
8	<a href="#">Prof Anna Latos-Bielenska</a>

**Table 5.3:** List of contributing EUROCAT Registries

EUROCAT Registry	Registry leader
INSERM U953, Hopital Saint Vincent de Paul, France	<a href="#">Dr Babak Khoshnood</a>
Registre Vaudois des Malformations Division Autonome de Genetique Medicale Switzerland	<a href="#">Dr Marie-Claude Addor</a>
Klinicka bolnica Sestre milosrdnice Klinika za dječje bolesti, Zagreb	<a href="#">Dr Ingeborg Barisic</a>
Malta Congenital Anomalies Registry Department of Health Information, Malta	<a href="#">Dr Miriam Gatt</a>
Provinciaal Instituut voor Hygiene, Belgium	<a href="#">Dr Vera Nelen</a>
Universitatskinderklinik Mainz, Germany	<a href="#">Dr Awi Wiesel</a>
Department of Public Health, Ireland	<a href="#">Dr Mary O'Mahony</a>
Medical Birth Registry of Norway	<a href="#">Dr Kari Klunysoyr</a>
Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty, Otto-von-Guericke University, Germany	<a href="#">Dr Anke Rissmann</a>
Registro Anomalias Congenitas CAV Direccion de Salud Publica, Spain	<a href="#">Dr Larraitz Arriola</a>

**Table 5.4:** List of advisory board members

Advisory board member	Country
Prof Gerard Visser	Netherlands
Dr Jim Morrow	UK
Dr Vibeke Backer	Denmark
Dr Hildrun Sunseth	Belgium
Dr Renzo Guerrini	Italy
Dr Saena Arbabzadeh-Bouchez	France
Prof Vincenzo Bettoli	Italy

## 6. Use and dissemination of foreground

**Table 6.1a:** List of all scientific publications relating to the foreground of the project.

LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS										
No	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers (if available)	Is/will open access be provided to this publication Yes/No
1	SSRI use before, during and after pregnancy: a population-based study in 6 European regions	Charlton	BJOG: An international journal of obstetrics and gynecology	Early view – online ahead of print	Blackwell Publishing	United Kingdom	2014		<a href="http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.13143/epdf">http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.13143/epdf</a>	Yes
2	Healthcare databases in Europe for studying medicine use and safety during pregnancy	Charlton	Pharmacoepidemiology and Drug Safety	Issue 23	John Wiley & Sons Ltd	United Kingdom	2014	586-594	<a href="http://onlinelibrary.wiley.com/doi/10.1002/pds.3613/epdf">http://onlinelibrary.wiley.com/doi/10.1002/pds.3613/epdf</a>	Yes
3	Major congenital anomalies in a Danish region	Garne	Danish Medical Journal	61(6)	The Danish Medical Association	Denmark	2014	NA	NA	Yes
4	Increased risk of severe congenital heart defects in offspring exposed to selective serotonin-reuptake inhibitors in early pregnancy – an epidemiological study using validated EUROCAT data	Knudsen	BMC pregnancy childbirth	14 (333)	BioMed Central	England	2014	NA	10.1186/1471-2393-14-333	Yes
5	Assessing the availability of the teratogenic drug isotretinoin outside the pregnancy prevention	Lagan	Pharmacoepidemiology and Drug Safety	Vol. 23/Issue 4	John Wiley and Sons Ltd	United Kingdom	01/04/2014	411-418	10.1002/pds.3565	Yes

	programme: a survey of e-pharmacies									
6	Drug safety in pregnancy--monitoring congenital anomalies.	Morgan	Journal of Nursing Management	19(3)	Blackwell publishing		2011	305-310		Yes
7	Antidepressant and psycholeptic use in pregnancy and risk of congenital anomaly: a European case-malformed control study	Boyle	In preparation							
8	Antiepileptic drug prescribing before, during and after pregnancy: a study in 7 European regions	Charlton	Pharmacoepidemiology and Drug Safety –under review							Yes
9	Asthma medication prescribing before, during and after pregnancy: a study in 7 European regions	Charlton	Journal of Allergy and Clinical Immunology – ready for submission							
10	Prescribing of antidiabetes medicines before, during and after pregnancy: a study in 7 European regions	Charlton	In preparation							
11	Electronic healthcare databases for evaluating pregnancy prevention programmes in Europe	Charlton	In preparation							
12	Insulin analogues in pregnancy and specific congenital anomalies; a literature review	De Jonge	Diabetes/Metabolism Research and Reviews – under review							Yes
13	Improving information on maternal medication use by linking prescription data to congenital anomaly registers: : A EUROmedicAT Study	De Jonge	In preparation							
14	Actual use of medications prescribed during pregnancy a cross-sectional	De Jonge	In preparation							

	study using data a population based congenital anomaly registry									
15	EUROmedicAT Recommendations: European Pharmacovigilance concerning Safety of Medication Use in Pregnancy	Dolk	In preparation							
16	Use of asthma-medication during pregnancy and risk of specific congenital anomalies – A European case-malformed control study	Garne	In preparation							
17	Risk of CA in Relation to Antiasthmatic Use: Population cohort Linkage Study	Garne	Journal of Allergy and Clinical Immunology – under review							
18	New signals of association between medication use in pregnancy and risk of congenital anomaly from the EUROmedicAT project	Given	In preparation							
19	SSRI use in pregnancy and risk of congenital anomaly: a population cohort linkage study in 3 countries	Jordan	In preparation							
20	EUROmedicAT data on medication use in pregnancy from congenital anomaly registries – a description	Loane	In preparation							
21	Signal detection relating to medication use in pregnancy and risk of congenital anomaly – development of a new methodology using EUROCAT registry data	Luteijn	In preparation							
22	A survey and focus group of women’s attitudes to the internet for medication purchase and safety information	Sinclair	In preparation							
23	Literature Review: new AED’s and the risk of congenital anomalies	Wang	In preparation							

24	Risk of orofacial clefts related to topiramate	Wang	In preparation							
25	Insulin analogues and Risk of Congenital Anomaly: a diabetic cohort study	Wang	In preparation							

**Table 6.1b:** List of all scientific conference abstracts relating to the foreground of the project.

<b>LIST OF SCIENTIFIC (PEER REVIEWED) ABSTRACTS</b>										
No	Title	Main author	Title of the periodical or the series	Number, date or frequency	Conference	Place of publication	Year of publication	Relevant pages	Permanent identifiers (if available)	Is/will open access be provided to this publication Yes/No
1	The EUROmedicAT central database	Loane	Pharmacoevidence and drug safety	To be determined	EUROmedicAT conference: Safety of Medication Use in Pregnancy					
2	Diabetes medication prescribing before, during and after pregnancy: a study in 7 European regions	Charlton	Pharmacoevidence and drug safety	To be determined	EUROmedicAT conference: Safety of Medication Use in Pregnancy					
3	Use of insulin analogs in pregestational diabetes and risk of congenital anomalies	Wang	Pharmacoevidence and drug safety	To be determined	EUROmedicAT conference: Safety of Medication Use in Pregnancy					
4	Antiepileptic drug prescribing before, during and after pregnancy: a study in 7 European regions	Charlton	Pharmacoevidence and drug safety	To be determined	EUROmedicAT conference: Safety of Medication Use in Pregnancy					
5	Use of Topiramate in relation to the risk of orofacial clefts	Wang	Pharmacoevidence and drug safety	To be determined	EUROmedicAT conference: Safety of Medication Use in Pregnancy					

6	The use of SSRI's in pregnancy: EUROMedicAT results	Charlton	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					
7	Linkage of prescription data to congenital anomaly registers to improve information on maternal medication use, a EUROMedicAT study	De Jonge	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					
8	Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in Pregnancy and Congenital Anomalies: analysis of 3 national linked databases	Jordan	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					
9	Selective Serotonin Reuptake Inhibitor (SSRI) Use in First Trimester Pregnancy and Risk of Congenital Anomalies: a EUROMedicAT case-malformed control study in 12 countries	Boyle	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					
10	Antiasthmatic drug use in pregnancy: EUROMedicAT results	Charlton	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					
11	Risk of congenital anomalies after exposure to asthma medication in the first trimester of pregnancy – a population cohort linkage study	Garne	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					
12	Use of asthma-medication during pregnancy and risk of specific congenital anomalies – A European case-malformed control study	Garne	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					
13	Online Purchasing of Medications from the Internet: Implications and Safety Issues	Sinclair	Pharmacoepidemiology and drug safety	To be determined	EUROMedicAT conference: Safety of Medication Use in Pregnancy					

14	EUROmedICAT pharmacovigilance: A systematic method of identifying potential teratogens	Luteijn	Pharmacoepidemiology and drug safety	To be determined	EUROmedICAT conference: Safety of Medication Use in Pregnancy					
15	New signals from EUROmedICAT	Given	Pharmacoepidemiology and drug safety	To be determined	EUROmedICAT conference: Safety of Medication Use in Pregnancy					
16	Building a sustainable reproductive pharmacovigilance system – recommendations from EUROmedICAT	Dolk	Pharmacoepidemiology and drug safety	To be determined	EUROmedICAT conference: Safety of Medication Use in Pregnancy					
17	SSRI use in pregnancy: a study in 6 European databases.	Jordan	Arch Womens Ment Health	18	International Marcé Society for Perinatal Mental Health Biennial Scientific Conference	2015	269–408 P.368	10.1007/S00737-014-0488-6		
18	EUROmedICAT Safety of Drugs in Pregnancy.	Jordan	Arch Womens Ment Health	18	International Marcé Society for Perinatal Mental Health Biennial Scientific Conference	2015	269–408 P.337	10.1007/S00737-014-0488-6		
19	Antiepileptic Drug Use before, during and after Pregnancy: A Study in 7 European Regions	Charlton	Pharmacoepidemiology and Drug Safety	23(s1)	The 30th International Conference of Pharmacoepidemiology & Therapeutic Risk Management	2014	S22	10.1002/pds.3701		
20	Healthcare Databases in Europe for Studying the Safety of Medicine Use during Pregnancy	Charlton	Pharmacoepidemiology and Drug Safety	22(s1)	The 29th International Conference of Pharmacoepidemiology & Therapeutic Risk Management	2013	S147	10.1002/pds.3512		
21	SSRI Use in Pregnancy: A Study in six European Databases	Charlton	Pharmacoepidemiology and Drug Safety	22(s1)	The 29th International Conference of Pharmacoepidemiology & Therapeutic Risk Management	2013	S365	10.1002/pds.3512		
22	EUROmedICAT: European Surveillance of Safety of	De Jong-van den	Pharmacoepidemiology and	20(s1)	27th International Conference on	2011	S46-S47	10.1002/pds.2206		Yes

	Medication Use in Pregnancy	Berg	Drug Safety		Pharmacoepidemiology & Therapeutic Risk Management				
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**Table 6.2:** List of all dissemination activities (publications, conferences, workshops, web sites/applications, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters).

LIST OF DISSEMINATION ACTIVITES								
NO	Type of activities	Main leader	Title	Date/Period	Place	Type of Audience	Size of audience	Countries addressed
1	Conference – poster	IFC-CNR	55th Annual meeting of the Teratology Society	27 June 2015	Montréal, Canada	Scientific community, Regulatory Authority		International
2	Seminar	IFC-CNR	EUROmedicAT: Uso e sicurezza dei farmaci in gravidanza.	10 June 2015	Tuscany, Italy	Regional Health Agency	30	Italy
3	Article	PUMS	Czy wszyscy mogą mieć zdrowe potomstwo?	May 2015	Wiedza i życie	Community		Poland
4	Conference – oral presentation	RUG	8 <sup>th</sup> international DIP symposium	15-18 April 2015	Berlin, Germany			
5	Web news item	IFC-CNR	Euromedicat news item on the Emilia Romagna Regional Health Authority Website	24 March 2015	Emilia Romagna, Italy	Health workers and the general public		Italy
6	Web news item	IFC-CNR	Second Euromedicat news item on the ARS Toscana - Agenzia regionale di sanità website	3 March 2015	Tuscany, Italy	Health workers and the general public		Italy
7	Web news item	IFC-CNR	EUROmedicAT news item on the Tuscany Registry of Congenital Defects website	19 March 2015	Tuscany, Italy	Neonatologists, Pediatricians, Obstetricians, Gynecologists, Geneticists involved in the Tuscany Registry of Congenital Defects and the general public		Italy

8	Web news item	IFC-CNR	EUROmedicAT news item on the Institute of Clinical Physiology-National Research Council website	19 March 2015	Tuscany, Italy	Institute workers and the general public		Italy
9	Newsletter	IFC-CNR	Newsletter of the Tuscany Registry of Congenital Defects. Content: main results of the EUROmedicAT project reported during the Conference in Poznan	19 March 2015	<a href="http://www.rtdc.it">http://www.rtdc.it</a>	Neonatologists, Pediatricians, Obstetricians, Gynecologists, Geneticists involved in the Tuscany Registry of Congenital Defects	120	Italy
10	Web news item	IFC-CNR	EUROmedicAT news item on the Environmental Epidemiology and Diseases Registries Unit website	19 March 2015	Tuscany, Italy	Institute workers and the general public		Italy
11	Web	IFC-CNR	Publication of the news regarding the EUROmedicAT results presented during the Conference in Poznan in the public website of the Rare Diseases Network of Tuscany	19 March 2015	<a href="http://www.malattierare.toscana.it">http://www.malattierare.toscana.it</a>			Italy
12	Web news item	IFC-CNR	EUROmedicAT news item on the Tuscany Registry of Rare Diseases website	19 March 2015	Tuscany, Italy	Health workers involved in the registry and the general public		Italy
13	Web	IFC-CNR	Publication of the news regarding the EUROmedicAT Conference in Poznan in the IFC website in the section Spotlight	11 March 2015	<a href="https://www.ifc.cnr.it/images/spotlight/2015/news1.pdf">https://www.ifc.cnr.it/images/spotlight/2015/news1.pdf</a>			Italy

14	Web	IFC-CNR	Publication of the news regarding the EUROmedICAT paper on SSRI in the IFC website in the section Spotlight	11 March 2015	<a href="https://www.ifc.cnr.it/index.php/it/spotlight/314-depressione-farmaci-e-rischi-per-il-feto">https://www.ifc.cnr.it/index.php/it/spotlight/314-depressione-farmaci-e-rischi-per-il-feto</a>			Italy
15	Web news item	IFC-CNR	First Euromedicat news item on the ARS Toscana - Agenzia regionale di sanità website	27 February 2015	Tuscany, Italy	Health workers and the general public		Italy
16	Scientific Abstract	IMER IFC-CNR	Pregnancy prevention programmes in Europe: A multi-disciplinary approach to isotretinoin use by women	13 February 2015	European Teratology Society. Amsterdam, 30 August-2 September 2015.	Scientific Community		Italy
17	Conference – 13 oral presentations	EUROmedICAT Steering Group	European Conference “Safety of Medication use in Pregnancy”	2-4 February 2015	Poznan, Poland	Scientific community, Regulatory Authority, Policy Makers/Politicians	650	International
18	Scientific Abstract	EUROmedICAT Steering Group	European Conference Booklet including abstract book “Safety of Medication use in Pregnancy”	2-4 February 2015	Poznan, Poland	Scientific community, Regulatory Authority, Policy Makers/Politicians	650	International
19	Conference – poster presentation	Schurman	European Conference “Safety of Medication use in Pregnancy”	2-4 February 2015	Poznan, Poland	Scientific community, Regulatory Authority, Policy Makers/Politicians	650	International
20	Leaflet	ULSTER	Projects EUROmedICAT Special Edition	2-4 February 2015	<a href="http://euromedicat.eu/content/EUROmedICAT%20Leaflet%202015.pdf">http://euromedicat.eu/content/EUROmedICAT%20Leaflet%202015.pdf</a>	Scientific community, Regulatory Authority, Policy Makers/Politicians	2000	International
21	Interview with Anna Latos-Bielenska	PUMS	Information about the EUROmedICAT European Conference Safety of Medication Use In Pregnancy	1 February 2015	Radio Mercury (Wielkopolska Region, Poland)	Community		Poland
22	Article	PUMS	Konferencja Europejska EUROmedICAT	February 2015	Fakty UMP	employees of Poznan University of Medical		Poznań

						Sciences		
23	Interview with Anna Latos-Bielenska	PUMS	about the EUROmedICAT European Conference Safety of Medication Use In Pregnancy	30 January 2015	Medexpress.pl	Health care professionals, policy makers, general public		Poland
24	Article in newspaper	PUMS	UM w Poznaniu: Konferencja o bezpieczeństwie leków stosowanych w ciąży	27 January 2015	Newspaper: Głos Wielkopolski, Poznan	Community, Media		Poland
25	Conference – oral presentation	RUG	The 30 <sup>th</sup> International Conference of Pharmacoepidemiology & Therapeutic Risk Management	24-27 October 2014	Taipei, Taiwan	Scientific community, Industry, Regulatory Authority		International – Europe, United States and Asia
26	Conference /oral presentation	ULSTER	EUROCAT post-marketing surveillance for congenital anomalies	21 October 2014	William Harvey Day 2014. London, UK	Academics, Students	150	UK
27	Publication	IFC-CNR	Inclusion of the EUROmedICAT leaflet in the Annual report 2014 with data for 2012	20 October 2014	<a href="http://rtcd.it/publicazioni.htm">http://rtcd.it/publicazioni.htm</a>	Neonatologists, Pediatricians, Obstetricians, Gynecologists, Geneticists involved in the Tuscany Registry of Congenital Defects	120	Italy
28	Conference /oral presentation	ULSTER	EUROCAT post-marketing surveillance for congenital anomalies	7 October 2014	BINOCAR scientific day. Swansea, UK	Scientists, Midwives	50	UK
29	Conference /poster presentation	SU	EUROmedICAT Safety of Drugs in Pregnancy. British Isles Network of Congenital Anomaly Registers (BINOCAR).	7 October 2014	BINOCAR scientific day. Swansea, UK			UK
30	Web	IFC-CNR	Publication of the news regarding the EUROmedICAT Conference in Poznan	25 September 2014	<a href="http://www.iss.it/cnmr">www.iss.it/cnmr</a>			Italy

31	Conference - workshop	SU	The International Marcé Society Scientific Conference	10-12 September 2014	Swansea, Wales	Service users, Healthcare professionals,		International
32	Presentation	UMCG	Linkage of prescription data to congenital anomaly registers to improve information on maternal medication use	September 2014	41st Annual meeting of the ICBDSR Helsinki, Finland	Scientific community, policy makers, other	60	worldwide
33	Conference – oral presentation and poster	RUG	EURODURG conference on drug utilisation research	27-29 August 2014	Groningen, The Netherlands	Scientific community, Industry, Regulatory Authority		International
34	Website	PUMS	EUROmediCAT European Conference Safety of Medication Use In Pregnancy website: <a href="http://www.euromedicatconference2015.eu/">http://www.euromedicatconference2015.eu/</a>	August 2014		Health care professionals, policy makers, general public		International
35	Leaflet	PUMS	EUROmediCAT European Conference Safety of Medication Use In Pregnancy leaflet	August-December 2014		Health care professionals	2000	International
36	Poster	PUMS	EUROmediCAT European Conference Safety of Medication Use In Pregnancy poster	August 2014 – January 2015		Health care professionals	45	Poland
37	Statement of the conference	PUMS	website poznan.pl	August 2014 – January 2015		Health care professionals, general community		Poland
38	Conference /oral presentation	ULSTER	Signal Detection methodology	27 June 2014	EUROCAT Registry Leaders Meeting. Belfast, UK	Scientists	50	UK
39	Oral presentation to a scientific event	ULSTER	Purchasing medications online: A teratogenic risk for pregnant women	1 June 2014	30th ICM Triennial Prague Congress. Czech Republic	Scientific community (higher education, Research) - Policy makers	1500	Worldwide
40	Presentation	UMCG	Linkage of prescription	June 2014	Teratology Society,	Scientific community,	50	USA, international

			data to congenital anomaly registers to improve information on maternal medication use		54th Annual Meeting Seattle, USA	policy makers, other		
41	Web	IFC-CNR ARS	Publication of the summary of the EUROmedICAT Conference in the Regional Health Agency (Agenzia Regionale di Sanità-ARS) website in the section Projects – Pharmacovigilance	24 February 2014	<a href="https://www.ars.toscana.it/it/aree-dintervento/cure-e-assistenza/farmacoepidemiologia/news/2925-e-sicuro-usare-farmaci-in-gravidanza-i-risultati-del-progetto-euromedicat.html">https://www.ars.toscana.it/it/aree-dintervento/cure-e-assistenza/farmacoepidemiologia/news/2925-e-sicuro-usare-farmaci-in-gravidanza-i-risultati-del-progetto-euromedicat.html</a>			Italy
42	Web	IFC-CNR	Linked EUROmedICAT website to the National Health Institute (Istituto Superiore di Sanità) website and publication of the news regarding General Meeting in Pisa	13 February 2014	<a href="http://www.iss.it/cnmr">www.iss.it/cnmr</a>			Italy
43	Web	IFC-CNR	Linked EUROmedICAT website to the Institute of Clinical Physiology website and publication of the news regarding General Meeting in Pisa	12 February 2014	<a href="http://www.iss.it/cnmr">www.iss.it/cnmr</a>			Italy
44	Website	PUMS	Dedicated Polish EUROmedICAT website	2014	<a href="http://mamapodopiek.a.pl/">http://mamapodopiek.a.pl/</a>	General public		Poland
45	Statement of the conference	PUMS	Regional Chamber of Nurses and Midwives in Poznan website	2014		Health care professionals		Poland
46	Statement of the conference	PUMS	Journal, Prenatal Cardiology Echo Płodu 2014, 3(14)	2014		Health care professionals		International
47	Oral presentation to a scientific event	IFC-CNR	Farmaci in gravidanza: progetto EUROmedICAT	25 December 2013	5th IMER training course	Scientific community (higher education, Research)		Italy

48	Organisation of Workshops	ULSTER	Medication Safety in Pregnancy	25 November 2013	Ulster University, UK	Pharmacists, medics, midwives, public health	100	UK
49	Oral presentation to a wider public	RUG	EUROmedicAT, Background and Goal of EUROmedicAT Study designs for signal detection and signal evaluation	22 October 2013	European Medicines Agency, London	Policy makers	50	European
50	Press releases	ULSTER	Nicht alle Medikamente sind für Schwangere schlecht	30 September 2013	<a href="http://www.welt.de/gesundheit/article120466458/Nicht-alle-Medikamente-sind-fuer-Schwangere-schlecht">http://www.welt.de/gesundheit/article120466458/Nicht-alle-Medikamente-sind-fuer-Schwangere-schlecht</a>	Civil society		Germany
51	Press releases	ULSTER	Eine ganz persönliche Entscheidung	29 September 2013	<a href="http://www.welt.de/print/wams/wissen/article120484844/Eine-ganz-persoenliche-Entscheidung.html">http://www.welt.de/print/wams/wissen/article120484844/Eine-ganz-persoenliche-Entscheidung.html</a>	Civil society		Germany
52	Oral presentation to a scientific event	ULSTER	EUROmedicAT: Safety of Medication use in pregnancy	27 September 2013	EUROleftnet Conference in Plodviv Bulgaria	Scientific community (higher education, Research)		European
53	Oral presentation to a scientific event	IFC-CNR	Congenital anomalies and oral retinoids: European Registry Study	13 September 2013	ACNE FERRARA 2013 - 11th Meeting on progress in Acne and related Dermatitis", Ferrara, Italy	Scientific community (higher education, Research) - Industry - Civil society		Italy
54	Posters	ULSTER	Purchasing medicines online: A study of Isotretinoin	3 September 2013	2013 International Pharmaceutical Federation (FIP) World Congress, Dublin, Ireland	Scientific community (higher education, Research) - Civil society	2000	Worldwide
55	Conference – oral presentation	Bath	The 29 <sup>th</sup> International Conference of Pharmacoepidemiology	25-28 August 2013	Montreal, Canada	Scientific community, Industry, Regulatory Authority		International – Europe, United States and Asia

	and poster		& Therapeutic Risk Management					
56	Oral presentation to a scientific event	RUG	Different study designs for signal detection and evaluation in pregnancy used in EUROmedicAT	14 June 2013	12th European Symposium on Congenital Anomalies. Zagreb, Croatia	Scientific community (higher education, Research)	100	European countries
57	Oral presentation to a scientific event	ULSTER	An evaluation of e-pharmacies selling the teratogenic drug, Isotretinoin	14 June 2013	12th European Symposium on Congenital Anomalies. Zagreb, Croatia	Scientific community (higher education, Research)	100	European Countries
58	Conference/poster	ULSTER	EUROmedicAT: Safety of Medication Use in Pregnancy in Relation to Risk of Congenital Anomalies	30 May 2013	University College Dublin	Scientific community	100	Europe
59	Posters	ULSTER	Purchasing medicines online: A study of Isotretinoin	3 April 2013	34th All Ireland Schools of Pharmacy conference, Cork, Ireland	Scientific community (higher education, Research)	200	Ireland
60	Web	IFC-CNR	Publication of the summary of the EUROmedicAT paper on SSRI in the Regional Health Agency (Agenzia Regionale di Sanità-ARS) website in the section Projects – Pharmacovigilance	10 March 2013	<a href="https://www.ars.toscana.it/it/aree-dintervento/cure-e-assistenza/farmacoepidemiologia/news/2940-le-donne-italiane-assumono-in-gravidanza-meno-antidepressivi-delle-donne-europee-risultati-dal-progetto-euromedicat.html">https://www.ars.toscana.it/it/aree-dintervento/cure-e-assistenza/farmacoepidemiologia/news/2940-le-donne-italiane-assumono-in-gravidanza-meno-antidepressivi-delle-donne-europee-risultati-dal-progetto-euromedicat.html</a>			Italy
61	Oral presentation to a wider public	RUG	EUROmedicAT: Geneesmiddelen en het risico op aangeboren afwijkingen	28 January 2013	University of Groningen Medical Center to midwives	Civil society		Netherlands
62	Lectures: A. Latos-	PUMS	Topics: EUROmedicAT; Maternal diabetes &	Academic year 2013-2014	University of Medical Sciences, Poznan,	Medicine, Midwifery, Nursing students	800	Poland

	Bielenska		pregnancy; Maternal epilepsy & pregnancy; Teratogenic influence of maternal medication during pregnancy; Reproductive health		Poland			
63	Lectures: A. Latos-Bielenska	PUMS	Topics: EUROMedicAT; Maternal diabetes & pregnancy; Maternal epilepsy & pregnancy; Teratogenic influence of maternal medication during pregnancy; Reproductive health	Academic year 2013-2014	PWSZ - Higher Vocational State School in Kalisz, Kalisz, Poland	Midwifery, Nursing students	400	Poland
64	Oral presentation to a scientific event	RUG	EUROMedicAT: a FP7 project for signal detection and evaluation of congenital anomalies	18 December 2012	Den Bosch to staff and workers of LAREB	Scientific community (higher education, Research)		Netherlands
65	Oral presentation to a scientific event	PUMS	EUROMedicAT: safety of medication use in pregnancy in relations to risk of congenital malformations	27 November 2012	Genes and Drugs Polish Pharmacogenetics congress PoznaD	Scientific community (higher education, Research)		Poland
66	Oral presentation to a scientific event	RUG	Different study designs for signal detection and evaluation in pregnancy, EUROMedicAT	22 November 2012	ENCEPP Plenary meeting	Scientific community (higher education, Research) - Industry - Policy makers		European
67	Oral presentation to a scientific event	ULSTER	The purchase of an online medication with known teratogenicity: a study of isotretinoin	13 November 2012	The Royal College of Midwives Annual Conference: Midwives Calling, Brighton, United Kingdom	Scientific community (higher education, Research) - Civil society	700	United Kingdom
68	Oral presentation to a scientific event	UMCG	Euromedicat: European surveillance of safety of medication use in pregnancy	30 October 2012	Joint ICBDSR and CCASN Annual Scientific Meeting, Ottawa, Canada	Scientific community (higher education, Research)	80	Worldwide
69	Oral presentation to	Bath	Using a primary care database to evaluate	11 October 2012	ENCEPP plenary meeting at the	Scientific community (higher education,	80	European

	a scientific event		drug safety in pregnancy: possibilities & limitations		European Medicines Agency. London, UK	Research)		
70	Presentations	UMCG	EUROmedICAT Safety of medication use in pregnancy	4 October 2012	2nd European Conference on Preconception Care, Rotterdam, the Netherlands	Scientific community (higher education, Research) - Policy makers	100	European countries
71	Posters	ULSTER	Online purchasing of Isotretinoin: E-pharmacies provision of safety information	27 August 2012	International Conference on PharmacoEpidemiology	Scientific community (higher education, Research) - Industry - Policy makers	1000	worldwide
72	Posters	SU	EUROmedICAT Safety of Drugs in Pregnancy	24 May 2012	Wellcome Collection: Thalidomide: A human tragedy: Marking the 50th anniversary of the withdrawal of	Scientific community (higher education, Research) - Civil society		United Kingdom
73	Presentations	UMCG	Postmarketing surveillance of medication use in pregnancy	17 May 2012	Epidemiology research meeting, Groningen, The Netherlands	Scientific community (higher education, Research)	25	Netherlands
74	Posters	ULSTER	Purchasing medicines online: A study of Isotretinoin	23 April 2012	Health Services Research and Pharmacy Practice Conference, University College Cork, Ireland	Scientific community (higher education, Research)	200	Ireland
75	Media briefings	ULSTER	Are asthma inhalers linked to birth defects?	11 March 2012	<a href="http://www.dailymail.co.uk/health/article-2113614/Are-asthma-inhalers-linked-birth-defects.html">http://www.dailymail.co.uk/health/article-2113614/Are-asthma-inhalers-linked-birth-defects.html</a>	Scientific community (higher education, Research) - Civil society		UK
76	Website	ULSTER	EUROCAT database as a Research Resource	17 January 2012	<a href="http://www.encepp.eu/encepp/viewResource.htm;jsessionid=ac10290cd11500ee9ba178744fba5d2b21b3ba48a2c.rlmOah8InljyqA4lpR9BcxaNb3i?id=2222">http://www.encepp.eu/encepp/viewResource.htm;jsessionid=ac10290cd11500ee9ba178744fba5d2b21b3ba48a2c.rlmOah8InljyqA4lpR9BcxaNb3i?id=2222</a>	Scientific community	unlimited	Global

77	Leaflet	ULSTER	EUROmedicAT Safety of Medication use in Pregnancy Project Leaflet	1 January 2012	University of Ulster	Scientific community (higher education, Research) - Industry - Civil society - Policy makers - Medias		International
78	Posters	PUMS	EUROmedicAT: European cooperation in the monitoring safety of medication use in pregnancy in relations to risk of congenital malformations	2 December 2012	The 7th Women's Health Forum Kalisz, Poland	Scientific community (higher education, Research) - Civil society	580	Poland
79	Oral presentation to a wider public	PUMS	Polish Registry of Congenital Malformations (PRCM) <sup>2</sup> its role in the health care system. Quality of data. Collaboration across the Europe	28 November 2011	The Conference of the Polish Presidency of the EU Council, Warsaw Poland	Scientific community (higher education, Research) - Civil society - Policy makers		Poland
80	Presentations	IFC-CNR	Health care databases for drug safety in pregnancy research	24 November 2011	Primary prevention of congenital malformations. Italian Network for folic acid promotion. Rome (Ital	Scientific community (higher education, Research)	100	Italy
81	Posters	PUMS	EUROmedicAT: safety of medication use in pregnancy in relations to risk of congenital malformations	4 November 2011	The 2nd International Conference - Promotion of Reproductive Health	Scientific community (higher education, Research)	200	Poland
82	Presentations	UMCG	SSRI gebruik tijdens zwangerschap 'SSRI use in pregnancy'	4 November 2011	Hospital Deventer, The Netherlands	Scientific community (higher education, Research)	50	Netherlands
83	Organisation of Workshops	IFC-CNR	An overview of EUROmedicAT project	21 October 2011	Residential course Congenital malformations: from prenatal diagnosis to postnatal therapy	Scientific community (higher education, Research)	80	Italy

					Viareggio			
84	Oral presentation to a scientific event	PUMS	Birth Defects in Central and Eastern Europe	24 September 2011	5th International Conference on Birth Defects & Disabilities in the Developing world Aódz, Poland	Scientific community (higher education, Research)		Worldwide
85	Posters	RUG	EUROmedicAT Safety of Medication use in pregnancy	25 August 2011	International Conference of PharmacoEpidemiology, Chicago, USA	Scientific community (higher education, Research) - Industry	1000	worldwide
86	Oral presentation to a wider public	PUMS	Urinary system malformations in Polish and European Registries (information on EUROmedicAT included)	17 June 2011	Neonatologists from neonatal care units, Poland	Scientific community (higher education, Research) - Civil society		Poland
87	Presentations	UMCG	EUROmedicAT Safety of medication use in pregnancy	7 June 2011	National Working Group on reproductive toxicology, Zeist, The Netherlands	Scientific community (higher education, Research)	25	Netherlands
88	Presentations	UMCG	EUROmedicAT Safety of medication use in Pregnancy	24 April 2011	National Committee on registration of Congenital Anomalies, The Hague, Netherlands	Scientific community (higher education, Research) - Policy makers	15	Netherlands
89	Oral presentation to a wider public	ULSTER	Presentation on EUROmedicAT	29 March 2011	Northern Ireland, FP7 Health Workshop run by Invest Northern Ireland	Scientific community (higher education, Research) - Industry - Civil society		United Kingdom
90	Presentations	ULSTER	An overview of EUROmedicAT WP7	28 March 2011	Maternal, Fetal and Infant Research Centre, University of Ulster, UK	Scientific community (higher education, Research)	12	Northern Ireland
91	Presentations	UMCG	EUROmedicAT Safety of medication use in Pregnancy	15 March 2011	Research meeting perinatal epidemiology, UMCG Groningen	Scientific community (higher education, Research)	20	Netherlands