Pharmacologie médicale

Pharmaco-épidémiologie
CIC Bordeaux CIC1401

EPIHAM

Epidemiology of acute hepatotoxicity from medicines

Study Protocol

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Eu2P PhD Programme – year 1

Doctoral Study Plan
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Eu2P PhD Trainee:
Prof. Sinem Ezgi Gülmez

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Eu2P PhD Thesis Coordinator:
Prof. Nicholas Moore
Professeur de Pharmacologie Clinique
MD, PhD, FRCP(Edin), FISPE

CENTRE COORDINATEUR
Service de Pharmacologie, Pharmaco-épidémiologie CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX – CHU de Bordeaux – Adera
Bâtiment Le Tondu – case 41
146 rue Léo Saignat – 33076 Bordeaux Cedex

HISTORY OF PROTOCOL UPDATES

Version	Date	Reason of update
V1.1	16/09/2014	Data extracton period for EGB after the comments by IDS (*Institut des Données de Santé*) Project duration after the comments by IReSP (Institut de Recherche en Santé Publique)
V1.2	18/03/2015	Update of dates and data extraction
V2.0	15/07/2015	Update of Calendar study

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1 SUMMARY

Study General Information	
1. Title	EPIHAM: Drug-induced liver injury leading to hospital admission: a study in national healthcare insurance databases.
2. Study code	EPIHAM (**Epi**demiology of acute **H**epa**a**totoxicity from **M**edicines)
3. Phase	IV: Pharmacoepidemiological study
4. Products of interest	All drugs
5. Study Rationale	Hepatotoxicity is one of the main causes of drug withdrawal from the market or discontinuation of drug development. It is also a major source of drug-induced hospital admissions and burden of care, with a risk of fatality of liver transplantation. Accordingly it is one of the main concerns of pharmacovigilance. Drug-induced hepatotoxicity can range from simple elevation of liver enzymes, to acute fulminant liver failure leading to death or liver transplantation. Simple asymptomatic elevation of liver enzymes is readily identified from clinical trials during drug development. It is usually dose and duration-dependent, and rarely results in actual clinical toxicity. Examples of this can be found for instance among non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, where increased transaminase concentrations can be found in up to 20% of patients. This increase is usually stable, and has no clinical symptoms. The transaminase increase subsided with drug discontinuation or sometimes if the drug is continued. Clinically significant increases in transaminases, accompanied with increased bilirubin, and clinical signs of hepatotoxicity such as jaundice, define Hy's law cases. It generally results in hospitalisation, and can be identified through hospital admission or discharge databases. A small number of cases may not be hospitalized and will resolve spontaneously when the drug is stopped. These will not be identified from the hospital discharge summaries, but at this time there is no way to identify non-hospitalized cases form the national healthcare insurance systems. They may be registered in medical records databases such as GPRD. In the UK the event rate for hepatic reactions leading to hospital admission, all drugs considered, was around 2.5 per 100 000 patient-years. This would represent about 1500 cases per year in a country like France.

6. Study design	The project relies on proven methodologies, already used in other settings to explore drug-related hepatotoxicity. The analysis of the association of the exposure to drugs identified in cases with the onset of hepatic injury will be assessed using several approaches: Case-population analysis The main study analysis will use the case-population approach, where the number of cases exposed to a given drug is compared to the number of subjects using the drug within the study time-frame, or to the number of defined daily doses (DDD) dispensed in the database population. This countrywide representative approach is the same as that used in the SALT study of ALFT, which included every liver transplantation center in seven countries. This ensured full inclusion of every case occurring in France, but only captured the most severe liver failures, not all liver injuries. The results found in the present study of hospitalized liver injuries will be compared to the fulminant hepatic failures studied in SALT. Both studies in fact complement each other, and will be able to compare for the same drugs the differences between hepatotoxicities leading only to hospitalisations, and those leading to transplantation. Case-crossover analysis One or more control periods will be selected, one year before the index date to take into account possible seasonal variations in drug use, or randomly within the year previous to the index date. The choice of the control period and the applicability of the case-crossover approach will be determined for each drug. Case-control analysis Within the database population, controls will be selected, matched on age, gender, concomitant chronic diseases (*Affection de Longue Durée*, ALD (Long Term Illness)). The feasibility of using propensity scores for the hepatic injury (not including possible exposures of interest) to select controls will be tested. The number of cases per control will be chosen on the order of magnitude of the expected odds ratio of the associations. As a first approximation, up to ten controls may be chosen for each case. Cohort analysis For selected at-risk drugs identified in the previous analyses and if events are many enough, incident user cohorts and controls, adjusted or matched on propensity scores will be built, and followed using cox proportional hazards analyses and survival curve functions to analyse the onset of hepatic injury.

7. Objectives Primary	• To identify the main drugs associated with DILIH in France and the event rates associated with DILIH, for individual drugs and for drug families, in terms of absolute and relative risks
Secondary	• To compare the event rates for non-transplantation DILIH and ALF in the national database with ALFT from transplantation centres, in terms of most commonly found medication and event rates (relative frequency of DILIH compared to ALFT), • To identify factors that might be associated with the severity of DILIH, including concomitant medication and diseases, • To develop methods that would allow for the systematic monitoring of DILI in France, for established and newly introduced drugs.
8. Expected number of cases	In France, the main population database for pharmacoepidemiology is SNIIRAM (*Système National d'Informations Inter-Régimes de l'Assurance Maladie*), which now covers about 97% of the French population. It covers over 60 million persons and is kept for 3 years plus on-going year. Because of database load lags, this represents about three years of full data including hospital data, *i.e.* about 180 million person-years. If needed three more years can be retrieved for a total of 360 million person-years of follow-up. However, using this very large database is complex, burdensome and time-consuming. The SNIIRAM has therefore developed a permanent 1/97 representative sample of the national database, called EGB, containing mostly the same information, and that is destined to accrue data on patients for 20 years. At the present time data is present since 2004 for all reimbursements, 2005 for hospital admission data, up to 2015 for reimbursement data and 2013 for hospital admissions. At the time of this project the hospital data will be current to 2013, resulting in 9 years of data.
9. Cases	Cases will be identified in the PMSI database by ICD-10-codes K71 (toxic liver disease) and K72 (hepatic failure, not elsewhere classified) as main diagnosis for hospital stay. (http://apps.who.int/classifications/icd10/browse/2010/en). - The main code of interest is K71 toxic liver disease: K71.0 toxic liver disease with cholestasis; K71.1 toxic liver disease with hepatic necrosis (and liver failure); K71.2 toxic liver disease with acute hepatitis; K71.6

	toxic liver disease with hepatitis, not elsewhere described would be the cases of prime interest. They will be studied separately and grouped. - K71.3 chronic persistent hepatitis; K71.4 chronic lobular hepatitis; K71.5 with chronic active hepatitis; K71.7 with fibrosis and cirrhosis of the liver; and K71.8 other disorders of the liver (peliosis, focal granular hyperplasia, hepatic granuloma, veno-occlusive disease of the liver would not be the prime objective of the study, but might be of interest in other studies. - K71.6 toxic liver disease with hepatitis not elsewhere classified, and K71.9, toxic liver disease, unspecified will be included in the sensitivity analyses, and so will K75.9 inflammatory liver disease, unspecified (hepatitis NOS). - Cases of acute hepatic injury related to viruses (B15-B19) or to acute alcoholic liver disease (K70.4), or to other acute liver diseases in K75, 76, or 77 may be used to identify drug utilisation related to the liver disease and symptoms itself, which could indicate protopathic bias. In the case-control approach such cases of non-toxic hepatic injury may also provide controls. Cases coded K71.1 toxic liver disease with hepatic necrosis, and K72.0 acute and subacute liver failure will be used to compare results with SALT, including K72.9 for sensitivity analysis. Cases that indicate these diagnostic codes as secondary diagnoses or associated diseases may also be included in sensitivity analyses. This excludes other causes of hepatic damage that have other specific ICD-10 codes.
10. Index date	The index date (ID) will be considered as the date of hospital admission for acute liver disease. Secondary index dates will be used for sensitivity analyses, 7 or 15 days prior to hospitalisation to take into account the clinical evolution of liver disease before hospital admission. Another index date considered will be the date of prescription of first liver function tests (transaminase) within a month before hospital admission, in patients without previous liver tests.
11. Exposure	A patient will be considered exposed to a drug with a dispensation date that makes it available within 30 days before index date: this covers all dispensation of drugs within 60 days before the index date for chronically used drugs. For drugs with intermittent use such as analgesics, the exposure date will be considered as dispensation within 30 days before index

	date, 60 days and 90 days. This is concordant with the 30-day timeframe for causality analysis as determined in the RUCAM method. No individual causality analysis will be done, since it is irrelevant in an epidemiological approach. All drugs will be considered and analysed, with special attention to the drug families found more commonly in SALT: paracetamol (ATC code N02BE01), anxiolytics and hypnotics (ATC code N05A, N05BB), antiepileptic drugs (ATC code N03A), NSAIDs (ATC code M01A), H1 antihistamines (ATC code R06), proton pump inhibitors (ATC code R06), antidepressants (ATC code N06A). For each patient considered as exposed, total exposure to suspect drugs within the previous year will be determined from dispensations, and measured in number of DDD dispensed within the year before Index date, as well as the duration of use before the index day for the hepatic injury.
12. Project duration Case inclusion period	24 months. 1st January 2009 - 31st December 2013.
13. Statistical analysis	Statistical analyses will be carried out using SAS software (SAS Institute, North Carolina, USA, current version), following the statistical analysis plan. Statistical analysis will be based on a case-population approach. • Descriptive analysis: The descriptive analysis for categorical and ordinal variables will provide the number and the frequency of each modality as well as missing data. The descriptive analysis for quantitative variables will provide mean, standard deviation, first quartile, median, third quartile, and extreme values. The 95% confidence interval (CI) will be presented for the most relevant parameters. • Case-population analysis: The main study analysis will use the case-population approach, where the number of cases exposed to a given drug is compared to the number of subjects using the drug within the study time-frame, or to the number of defined daily doses (DDD) dispensed in the database population (accessed February 12th 2014 http://www.whocc.no/atc_ddd_index/). From the distribution of drug utilisation in the general population, and that of the cases, hazard function curves will be built using standard processes. • Case-crossover analysis: One or more control periods will be selected, one year before the index

	date to take into account possible seasonal variations in drug use, or randomly within the year previous to the index date. • Case-control analysis: Within the database population, controls will be selected, matched on age, gender, concomitant chronic diseases (ALD). The feasibility of using propensity scores for the hepatic injury (of course not including possible exposures of interest) to select controls will be tested. • Cohort analysis: For selected at-risk drugs identified in the previous analyses and if events are many enough, incident user cohorts and controls, adjusted or matched on propensity scores will be built, and followed using cox proportional hazards analyses and survival curve functions to analyse the onset of hepatic injury.
14. Expected results	The results of this study could lead to the identification of potentially hepatotoxic agents that have not yet been recognized. This may lead to regulatory intervention, or to changes in the understanding of drug-induced hepatotoxicity. If new hepatotoxic drugs are discovered, this could open the way to translational studies looking at hepatotoxic mechanisms, including genetic predisposition for certain types of hepatotoxic drugs. The understanding of hepatotoxic risk factors or predisposition will help the regulatory agencies inform users and prescribers of potential risks and risk factors, which would ultimately help the Agency make drugs safer for the end users. Finally the various sensitivity analysis will help to better understand the methodologies for this kind of study in teh national databases, which could result in systematic and routine monitoring of drug-induced hepatotoxicity in the national healthcare system reimbursement database.
15. Ethics, Data Confidentiality, Patient Protection and Good Practices	This study will be done according to good pharmacoepidemiology practises as described by ISPE (www.pharmacoepi.org) and will comply with all relevant legislation concerning data protection. This study will be developed according to the European Network of Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct and methodological standards guide, and the study will be registered in ENCePP database. Study protocol and results will also

	be made public according to ENCePP requirements.
16. Strengths & Limitations Strengths	The methodology relies on proven bases and new initiatives: The case-population methodology is efficient for this type of very rare event with 100% ascertainment rates.
Limitations	• Lack of power in EGB: This could be exploited in SNIIRAM database. • Coding errors: Sensitivity analyses will be performed. • Poor recording of occasional medication (*e.g.* paracetamol) or toxic exposure (*e.g.* alcohol): In France over 80% of paracetamol use is prescription, and is recorded in the database. It is possible that instances of paracetamol exposure may be missed in non-overdose cases (there is a specific ICD-10 code for liver failure related to drug overdose). There is no reason for that to occur more of less frequently in patients with or without liver injury. Non-differential misclassification of exposure would in fact be conservative for paracetamol. Acute alcoholic liver injury also has a specific ICD code. This will be included in the sensitivity analyses, to test for interactions for instance between alcohol-related diagnoses and paracetamol for liver injury.

2 LIST OF ABBREVIATIONS

ADERA	*Association pour le Développement de l'Enseignement et des Recherches auprès des universités, des centres de Recherche et des entreprises d'Aquitaine*
ALD	*Affection de Longue Durée* (Long Term Illness)
ALF	Acute Liver Failure
ALFT	Acute Liver Failure leading to registration for Transplantation
ATC	Anatomic-Therapeutic-Chemical
AvDD	Average Daily Dose
CCAM	*Classification Commune des Actes Médicaux*
CNAMTS	*Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés*
CNIL	*Commission Nationale de l'Informatique et des Libertés*
DDD	Defined Daily Dose
DILI	Drug Induced Liver Injury
DILIH	Drug Induced Liver Injury leading to Hospital admission
HAS	*Haute Autorité de Santé*
EGB	*Echantillon Généraliste des Bénéficiaires*
ICD-10	International Statistical Classification of Diseases, 10th revision
ID	Index Date
IDS	*Institut des Données de Santé*
INSEE	*Institut National de la Statistique et des Etudes Economiques*
INSERM	*Institut National de la Santé Et de la Recherche Médicale*
IReSP	*Institut de Recherche en Santé Publique*
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
LPP	*Liste des Produits et Prestations*
MPR	*Medication Possession Rate*
MSA	*Mutualité Sociale Agricole*
PMSI	*Programme Médicalisé des Systèmes d'Informations* (French National Hospital Discharge Summaries Database)
RNIAM	*Répertoire National Inter-régimes des bénéficiaires de l'Assurance Maladie*
RSI	*Régime Social des Indépendants*
SALT	Study of Acute Liver Transplant
SNIIRAM	*Système National d'Informations Inter-Régimes de l'Assurance Maladie*
TNB	*Table Nationale de Biologie*

3 PHD THESIS RESEARCH PROJECT SUPERVISION

This Eu2P PhD project will be conducted under the overall supervision and coordination of the tutor, Prof. Nicholas Moore.

Prof. S. Ezgi Gulmez, the scientific coordinator, will manage the study. She will be in charge of development and validation of study documentation, data extraction strategies, data analysis plan, monitoring of data analysis, generation of the study report and publications.

An operational team made of a study manager, one chief statistician, and data manager will assist the study.

4 STUDY FINANCE

Financing of the study is obtained through a joint help from *Direction Générale de la Santé* (DGS), *from Mission recherche de la Direction de la recherche, des etudes, de l'évalusation et des statistiques* (MiRe-DREES) of *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (CNAMTS), *Régime Social Indépendants* (RSI) and *Caisse Nationale de Solidarité pour l'Autonomie* (CNSA), as part of the general call for projects by IReSP (*Appel à Projets, Institut de Recherche en Santé Publique*) in 2013.

5 STUDY PROJECT TEAM

Prof Mathieu Molimard (Head of Department)	Service de Pharmacologie Pharmaco-épidémiologie CIC Bordeaux CIC 1401 INSERM-Université de Bordeaux-CHU de Bordeaux INSERM U657 - Case 36 146, Rue Leo Saignat, 33076 Bordeaux Cedex France Tel: +33 55757 1060 / Fax +33 55757 4671 E-mail: mathieu.molimard@u-bordeaux.fr
Prof Nicholas Moore (Head of CIC1401, PhD supervisor)	Service de Pharmacologie Pharmaco-épidémiologie CIC Bordeaux CIC 1401 INSERM-Université de Bordeaux-CHU de Bordeaux INSERM U657 - Case 36 146, Rue Leo Saignat, 33076 Bordeaux Cedex France Tel: +33 55757 1560 – 4673 / Fax +33 55757 4671 E-mail: nicholas.moore@u-bordeaux.fr
Assoc Prof S. Ezgi Gülmez (Scientific Coordinator, PhD trainee)	Service de Pharmacologie Pharmaco-épidémiologie CIC Bordeaux CIC 1401 INSERM-Université de Bordeaux-CHU de Bordeaux Case 41-146, rue Léo Saignat, 33076 Bordeaux Cedex France Tel: +33 (0) 55757 9564 / Fax: +33 (0) 55757 4740 E-mail: sinem-ezgi.gulmez@u-bordeaux.fr
Cécile Droz-Perroteau (Chief operating officer)	Service de Pharmacologie Pharmaco-épidémiologie CIC Bordeaux CIC 1401 INSERM-Université de Bordeaux-CHU de Bordeaux Case 41-146, rue Léo Saignat, 33076 Bordeaux Cedex France Tel: +33 (0) 55757 4737 / Fax: +33 (0) 55757 4740 E-mail: cecile.droz@u-bordeaux.fr
Adeline Grolleau (Project Manager Assistant)	Service de Pharmacologie Pharmaco-épidémiologie CIC Bordeaux CIC 1401 INSERM-Université de Bordeaux-CHU de Bordeaux Case 41-146, rue Léo Saignat, 33076 Bordeaux Cedex France Tel: +33 (0) 55757 9203 / Fax: +33 (0) 55757 4740 E-mail: adeline.grolleau@u-bordeaux.fr
Régis Lassalle (Statistician and Data Management Manager)	Service de Pharmacologie Pharmaco-épidémiologie CIC Bordeaux CIC 1401 INSERM-Université de Bordeaux-CHU de Bordeaux Case 41-146, rue Léo Saignat, 33076 Bordeaux Cedex France Tel: +33 (0) 55757 4764 / Fax: +33 (0) 55757 4740 E-mail: regis.lassalle@u-bordeaux.fr
Anaïs Chartier (Statistician-SAS programmer©)	Service de Pharmacologie Pharmaco-épidémiologie CIC Bordeaux CIC 1401 INSERM-Université de Bordeaux-CHU de Bordeaux Case 41-146, rue Léo Saignat, 33076 Bordeaux Cedex France Tel: +33 (0) 55757 4768 / Fax: +33 (0) 55757 4740 E-mail: anais.chartier@u-bordeaux.fr

6 INTRODUCTION

Hepatotoxicity is one of the main causes of drug withdrawal from the market or discontinuation of drug development. It is also a major source of drug-induced hospital admissions and burden of care, with a risk of fatality of liver transplantation. Accordingly it is one of the main concerns of pharmacovigilance. (1-3)

Drug-induced hepatotoxicity can range from simple elevation of liver enzymes, to acute fulminant liver failure leading to death or liver transplantation. Simple asymptomatic elevation of liver enzymes is readily identified from clinical trials during drug development. It is usually dose and duration-dependent, and rarely results in actual clinical toxicity. Examples of this can be found for instance among NSAIDs with drugs such as diclofenac, where increased transaminase concentrations can be found in up to 20% of patients. This increase is usually stable, and has no clinical symptoms. The transaminase increase subsided with drug discontinuation or sometimes if the drug is continued.

Clinically significant increases in transaminases, accompanied with increased bilirubin, and clinical signs of hepatotoxicity such as jaundice, which define Hy's law cases. It generally results in hospitalisation, and can be identified through hospital admission or discharge databases. A small number of cases may not be hospitalized and will resolve spontaneously when the drug is stopped. These will not be identified from the hospital discharge summaries, but at this time there is no way to identify non-hospitalized cases form the national healthcare insurance systems. They may be registered in medical records databases such as GPRD. (4) In the UK the event rate for hepatic reactions leading to hospital admission, all drugs considered, was around 2.5 per 100 000 patient-years. This would represent about 1500 cases per year in a country like France.

Finally fulminant hepatitis or acute liver failure is accompanied by signs of liver insufficiency such as neurological symptoms and coma, bleeding through defective synthesis of coagulation factor. It can lead to death if the patient does not receive a hepatic transplantation. These liver failures can be identified through the liver transplantation units, which register exhaustively all patients registered for liver transplantation. Such procedures cannot be performed outside agreed centres. In the SALT study of NSAID associated acute liver failure leading to registration for transplantation (ALFT), the event rate was about 0.5 per million person-years. (5)

The identification of cases of ALFT is very direct, since all cases are registered. One must then retrieve the information from the clinical files, including on previous drug exposure. The main issue is the small number of cases: even though they are the most relevant from a public

health point of view, because contrary to many other adverse drug reactions of concern such as myocardial infarction, surviving non-transplanted acute hepatic injury will recover completely in the vast majority of cases, excluding chronic fibrotic reactions that are more common for viral hepatitis where the injurious agent persists. However the very small number of cases makes precise analyses of event rates uncertain. It would therefore be more meaningful to study serious hepatic reactions leading to hospital admission. Because of the multiplicity of sites where such cases might be recorded or admitted, field studies are very uncertain and may be extremely time and manpower-intensive. It would therefore be preferable to access cases directly from population-wide databases.

At the present time there is no systematic approach to the identification and quantification of drug-related hepatotoxicity for drugs that are already marketed, and most signals are developed from spontaneous reporting, with a large uncertainty because of variable under-reporting. At the same time most of the concern is on the toxicity of new drugs that are coming on to the market, whereas most probably the greatest healthcare burden may well be from old drugs with known hepatic risks or from unrecognized drug-related risks.

A previous multinational case-population field study of NSAIDs-associated acute liver failure leading to registration for transplantation (ALFT), (5) led to the conclusions that i) ALFT is a very rare event (0.5 per million inhabitants over three years in Europe), (5) ii) Event rates may be expressed per patient years exposed or per number of actual patients, the choice between the two being related to the mechanism of the adverse reaction and the hazard function, (6) iii) many drugs other than NSAIDs are involved in ALFT, including therapeutic-dose paracetamol. (5)

In France where per-user information was available, there was about 0.4 cases per million persons exposed, similar for all NSAIDs. (6) Paracetamol, which is known to be hepatotoxic in overdose, was also associated with a significantly higher rate of ALFT without overdose, both per million patient-years (3.3 per million patient-years) and per user (1.5 per million persons exposed). The French data also showed that there were higher per user or per patient-year or DDD rates of ALFT associated with other drugs such as some benzodiazepines, or antiepileptic drugs. The total number of events was low, but these as yet unpublished results warrant further validation and verification, especially when event rates can vary 100-fold within products in the same drug families. Beyond the continuation of the exploration of ALFT and the drugs involved in fulminant hepatitis, it would seem important to verify whether these drugs are also involved in less severe hepatotoxicity, still resulting in hospital admission.

This study, EPIHAM, will be done within the French national health care systems databases, which include all reimbursed health-care expenses, and all hospital admissions with ICD-10 coded admission diagnoses. The overall methodological approach will be initially that of a case-population study to compare event rates with those found in SALT. This will be completed by other methods: a case-crossover approach, a classical case-control study, and a propensity-score adjusted or matched cohort study of products selected from the case-population data.

The routines created for this project may be reused to set up regular surveillance of drug-related hepatic disorders in the French population.

7 STUDY OBJECTIVES

The primary objective is:

- To identify the main drugs associated with DILIH in France and the event rates associated with DILIH, for individual drugs and for drug families, in terms of absolute and relative risks.

The secondary objectives are:

- To compare the event rates for non-transplantation DILIH and ALF in the national database with ALFT from transplantation centres, in terms of most commonly found medication and event rates (relative frequency of DILIH compared to ALFT),
- to identify factors that might be associated with the severity of DILIH, including concomitant medication and diseases,
- to develop methods that would allow for the systematic monitoring of DILI in France, for established and newly introduced drugs.

The results of this study could lead to the identification of potentially hepatotoxic agents that have not yet been recognized, and that may lead to regulatory intervention, or to changes in the understanding of drug-induced hepatotoxicity. If new hepatotoxic drugs are discovered, this could open the way to translational studies looking at hepatotoxic mechanisms, including genetic predisposition for certain types of hepatotoxic drugs. The understanding of hepatotoxic risk factors or predisposition will help the regulatory agencies inform users and prescribers of potential risks and risk factors, which would ultimately help the Agency make drugs safer for the end users.

8 METHODOLOGY

8.1 GENERAL STUDY DESIGN

EPIHAM is a case-populations study, with secondary variations, of cases of patients admitted with a primary diagnosis of acute toxic liver injury.

The scientific project is to identify in the national healthcare databases all hospital admissions for toxic or unexplained liver injuries. From these cases, drug exposures within the month preceding index date will be considered, and compared to population exposure to the same drugs (case-population approach) or to more specific methods such as case-crossover or case-control methods. Within drug classes, a cohort approach based on high-dimensional propensity score adjustment or matching may be attempted.

8.2 DATA SOURCES IN FRANCE

In France, the main population database for pharmacoepidemiology is SNIIRAM (*Système National d'Informations Inter-Régimes de l'Assurance Maladie*), which now covers about 97% of the French population. It includes all medical expenses that are eligible for coverage by the national health system, including medical consultations, drugs dispensed (quantity and type), private practice hospital admissions and procedures, and also the exact lab tests prescribed and performed but not the results. It also includes information on a number of chronic diagnoses that warrant full coverage of all expenses related to those diseases (ALD). This base is linked to the hospital discharge summaries database (PMSI), and to the death registry, which provides date of death but not cause of death. Hospital discharge summaries provide main and secondary diagnoses coded in ICD-10, as well as dates of hospital admission and discharge.

The main SNIIRAM database, which covers over 60 million persons, is kept for three years plus on-going year (*i.e.* at this time 2012-2014 plus 2015). Hospital data is downloaded and linked with a few months' delay, so that the previous year's data is downloaded and linked in end of Q2 for the previous year. This means that in Q3 of the current year, all information pertaining to the previous 3 years is available. Because of database load lags, this represents about three years of full data including hospital data, *i.e.* about 180 million person-years. If needed, three more years can be retrieved for a total of 360 million person-years of follow-up.

However, using this very large database is complex, burdensome and time-consuming. The SNIIRAM has therefore developed a permanent 1/97 representative sample of the national database, called EGB, containing mostly the same information, and that is destined to accrue data on patients for 20 years. At the present time data is present since 2004 for all

reimbursements, 2005 for hospital admission data, up to 2015 for reimbursement data and 2013 for hospital admissions. At the time of this project the hospital data will be current to 2013, resulting in nine years of data.

These databases include all reimbursed healthcare expenses, such as drug dispensations, medical and non-medical consultations and procedure expenses, lab tests etc. The main reimbursement database includes no clinical information except a number of long-term diseases that open rights to full reimbursement of all expenses related to the disease, such as diabetes, cancer or ischemic heart disease.

This database is linked to the hospital discharge summary database (PMSI), which includes primary and secondary diagnoses, and procedures linked to individual hospital stays. It is also linked to the national death registry that provides the patients' date of death, if relevant. Causes of death are not yet linked.

The Department of Pharmacology of Bordeaux, through its INSERM CIC Bordeaux CIC1401 Pharmacoepidemiology Unit, has its legally authorized access to the 1/97 EGB sample, under condition that a protocol is declared to INSERM-SNIIRAM. Access to the full SNIIRAM database requires authorisation from CNIL, the French Data Protection Agency, and authorisation from *Institut des Données de Santé* (IDS), an independent entity that by law supervises proper access to the SNIIRAM data.

8.3 CASES

8.3.1 CASE IDENTIFICATION

The main previous obstacle for the use of these methods in population databases was the use of ICD-9CM codes, which were not specific for different types of liver diseases. ICD-10 coding provides much more specific codes for toxic liver disease and for other cause-specific diseases that would be excluded from the study.

Cases will be identified in the PMSI database by ICD-10 codes K71 (toxic liver disease) which includes drug-induced liver disease, and K72 (hepatic failure, not elsewhere classified) (accessed February 12th 2014, http://apps.who.int/classifications/icd10/browse/2010/en):

- The main code of interest is K71 toxic liver disease:

K71.0 toxic liver disease with cholestasis; K71.1 toxic liver disease with hepatic necrosis (and liver failure); K71.2 toxic liver disease with acute hepatitis; K71.6 toxic liver disease with hepatitis, not elsewhere described would be the cases of prime interest. They will be studied separately and grouped.

- K71.3 chronic persistent hepatitis; K71.4 chronic lobular hepatitis; K71.5 with chronic active hepatitis; K71.7 with fibrosis and cirrhosis of the liver; and K71.8 other disorders of the liver (peliosis, focal granular hyperplasia, hepatic granuloma, veno-occlusive disease of the liver would not be the prime objective of the study, but might be of interest in other studies.
- K71.6 toxic liver disease with hepatitis not elsewhere classified, and K71.9, toxic liver disease, unspecified will be included in the sensitivity analyses, and so will K75.9 inflammatory liver disease, unspecified (hepatitis NOS).
- Cases of acute hepatic injury related to viruses (B15-B19) or to acute alcoholic liver disease (K70.4), or to other acute liver diseases in K75, 76, or 77 may be used to identify drug utilisation related to the liver disease and symptoms itself, which could indicate protopathic bias. In the case-control approach such cases of non-toxic hepatic injury may also provide controls.

Cases coded K71.1 toxic liver disease with hepatic necrosis, and K72.0 acute and subacute liver failure will be used to compare results with SALT, including K72.9 for sensitivity analysis. Cases that indicate these diagnostic codes as secondary diagnoses or associated diseases may also be included in sensitivity analyses. This excludes other causes of hepatic damage that have other specific ICD-10 codes.
The aim of the study is specificity more than sensitivity, to explore possible associations of drugs with toxic liver disease. Misclassification would reduce the number of cases and reduce overall study power, but not alter the results if misclassification is not related to exposure. This might be the case for drugs that are known to be associated with hepatic injury, which would be classified in K71.2, whereas cases exposed to drugs not known to be (or presumed not to be) associated with hepatotoxicity might be coded as K75.9, hepatitis NOS. The sensitivity analyses will also include these cases. It is expected that in a hospital environment a case of jaundice should be properly classified into the appropriate hepatic code category. In the same was, a simple increase in transaminase without clinical symptoms would not warrant a hospital admission and/or would not be included as main diagnosis for hospital admission.
Individual cases cannot be validated since all the data in the database are anonymous. Smaller field studies have validated the codes in the PMSI against individual patients. The diagnostic codes used are the same as those tested in the EU-ADR project, and confirmed by OMOP. (7-9)

8.3.2 EXPECTED NUMBER OF CASES

In France, the main population database for pharmacoepidemiology is SNIIRAM (*Système National d'Informations Inter-Régimes de l'Assurance Maladie*), which now covers about 97% of the French population. It covers over 60 million persons and is kept for 3 years plus on-going year. Because of database load lags, this represents about three years of full data including hospital data, *i.e.* about 180 million person-years. If needed three more years can be retrieved for a total of 360 million person-years of follow-up. However, using this very large database is complex, burdensome and time-consuming. The SNIIRAM has therefore developed a permanent 1/97 representative sample of the national database, called EGB, containing mostly the same information, and that is destined to accrue data on patients for 20 years. At the present time data is present since 2004 for all reimbursements, 2005 for hospital admission data, up to 2015 for reimbursement data and 2013 for hospital admissions. At the time of this project the hospital data will be current to 2013, resulting in 9 years of data.

8.4 CASE INCLUSION PERIOD

The case inclusion period in the cohort is between 1st January 2009 and 31st December 2013.

8.5 INDEX DATE

Index date (ID) will be considered as the date of hospital admission for acute liver disease.
Secondary IDs will be used for sensitivity analyses, 7 or 15 days prior to hospitalisation to take into account the clinical evolution of liver disease before hospital admission. Another index date considered will be the date of prescription of first liver function tests (transaminase) within a month before hospital admission, in patients without previous liver tests.

8.6 EXPOSURE

Exposures will be classified as the ATC code of the drug dispensed, and the quantity dispensed in number of DDD (defined daily doses).
A case will be considered exposed to a drug with a dispensation date that makes it available within 30 days before ID. This covers all dispensation of drugs within 60 days before the ID for chronically used drugs. For drugs with intermittent use such as analgesics, the exposure date will be considered as dispensation within 30 days before ID, 60 days and 90 days. This is concordant with the 30-day timeframe for causality analysis as determined in the RUCAM method.

Drugs will be considered singly, in the absolute, and compared to other drugs in their ATC class. ATC classes as a whole may be considered also as a whole, depending on the number of cases exposed to a given class and to individual drugs within a class. All drugs will be considered and analysed, with special attention to the drug families found more commonly in SALT: paracetamol (ATC code N02BE01), anxiolytics and hypnotics (ATC code N05A, N05BB), antiepileptic drugs (ATC code N03A), NSAIDs (ATC code M01A), H1 antihistamines (ATC code R06), proton pump inhibitors (ATC code R06), antidepressants (ATC code N06A).

For each patient considered as exposed, total exposure to suspect drugs within the previous year will be determined from dispensations. Exposure after dispensation will be considered to last 1.25 times the number of DDD dispensed for drugs with chronic use, twice the number of DDD dispensed for drugs with intermittent or occasional use such as analgesics or NSAIDs, and to the number of DDD dispensed for drugs with acute use such as antibiotics. More specific exposure rules may be devised for specific drugs (*i.e.*, vaccines) if needed, using advice from our Department's ad-hoc scientific advisory group.

The beginning of a treatment episode is considered for the first dispensation after at least 90 days without any dispensation of the drug of interest.

8.7 DATA EXTRACTION

Cases will first be identified in EGB, and described, as well as their exposures. From these, the power of the EGB analysis will be determined for the various drug families. If power is insufficient in EGB, access to SNIIRAM will be requested. Because of the different nature of EGB and SNIIRAM, especially concerning the size of the database and the duration of the follow-up included in the database, some of the elements of the analysis may need to be changed. This would primarily concern long-term follow-up for accumulation toxicity, but would not affect the identification of most instances of acute hepatotoxicity, which usually occurs early during treatment (except maybe for a few select drugs such as diclofenac, flucloxacillin and sulphalazine).

Even if cases are identified and retrieved from SNIIRAM, population data and controls in the case-control analysis would be identified in EGB. There would be no selection or identification bias from using controls from EGB in the case-control analysis or in the case-population analysis. In the case-crossover, all information would be retrieved from the same database, EGB or SNIIRAM.

The routines used to identify cases and exposures will be developed in EGB, and used identically in SNIIRAM if needed.

For all subjects meeting the eligibility criteria, the following data will be extracted from EGB:

- Socio-demographic data: age, gender, year of birth, month and year of death, date of insertion in EGB,
- ALD data: "ALD 30" codes and associated ICD-10 codes, ALD start date and ALD end date,
- Hospitalization data of the PMSI from 2005 - 2013: date of entry and exit of hospitalization, length of stay, main diagnosis and associated diagnosis codes, medical procedures performed during the stay (CCAM),
- Healthcare reimbursement data from 2005 - 2013: prescription and delivery dates, category of service (medical or paramedical consultation, acts of biology, medical procedure, medical device, transport, *etc.*) CIP code and ATC code of delivered drugs, number of units dispensed, detailed codes of lab tests (TNB), medical devices (LPP), and medical procedure nomenclatures (CCAM) and prescriber characteristics.

9 ADVERSE EVENT REPORTING

Since the study is a non-interventional study, which is based on secondary use of data, the reporting of suspected adverse reactions is not required.

10 STATISTICAL ANALYSIS

Statistical analyses will be carried out using SAS software (SAS Institute, North Carolina, USA, current version), following the statistical analysis plan.

The main analysis is the case-population analysis (10) with event rates expressed per million users for idiosyncratic reactions occurring early during treatment, to avoid the healthy survivor effect. If the reaction shows indications of being dose or duration-dependent, event rates will be expressed per billion DDD dispensed.

For the other analyses, the methodology is standard and used routinely in our Department.

Case-control studies will select controls based on various matching methods, from comparison with full population using no matching (the case-population approach), to progressively increasing matching complexity, then using first the simplest matching (age and sex, presence in the database at time of case index date), and progressively more complex matching, including on associated diseases, or burden of care. Controls may also include cases (as in the case-population study), or exclude subjects that have been cases, but not

future cases, or exclude all patients that ever become cases. Using these various control definitions in sensitivity analysis will help ascertain the robustness of the results.

10.1 DESCRIPTIVE ANALYSIS

The descriptive analysis for categorical and ordinal variables will provide the number and the frequency of each modality as well as missing data. The descriptive analysis for quantitative variables will provide mean, standard deviation, first quartile, median, third quartile, and extreme values. The 95% confidence interval (CI) will be presented for the most relevant parameters.

For comparisons between groups, the significance level of statistical tests will set at 5% in bilateral formulation. The following tests will be used:

- For categorical and ordinal variables: Pearson Chi-2 test or Fisher's exact test if the theoretical numbers are less than 5,
- For quantitative variables between two independent groups: Student's t-test if the hypotheses of distributions normality and homoscedasticity of variances are validated or otherwise nonparametric Wilcoxon rank test,
- For quantitative variables between more than two independent groups: analysis of variance if the hypotheses of distributions normality and homoscedasticity of variances are validated or otherwise Kruskal-Wallis test.

10.2 CASE-POPULATION ANALYSIS

The main study analysis will use the case-population approach, (10)where the number of cases exposed to a given drug is compared to the number of subjects using the drug within the study time-frame, or to the number of defined daily doses (DDD) dispensed in the database population (accessed February 12th 2014 http://www.whocc.no/atc_ddd_index/). This approach is the same as that used in the SALT study of ALFT. (5, 6, 11) It will allow comparing the event rates for hospitalized liver injury and that of ALFT for the same products over the same period in the same population. This also allows for event rate comparisons between different drugs of the same class, or between drugs used for the same indications.

From the distribution of drug utilisation in the general population, and that of the cases, hazard function curves will be built using standard processes.

10.3 CASE-CROSS-OVER ANALYSIS

One or more control periods will be selected, one year before the index date to take into account possible seasonal variations in drug use, or randomly within the year previous to the

index date. The choice of the control period and the applicability of the case-crossover approach will be determined for each drug class: it might be applicable for short-term use drugs such as analgesics or antibiotics, but not for long-term use drugs like anti-epileptic or antihypertensive drugs. The analysis will be done using logistic regression on discordant paired periods. (12, 13)

10.4 CASE-CONTROL ANALYSIS

Within the database population, controls will be selected, matched on age, gender, concomitant chronic diseases (*Affection de Longue Durée*, ALD (Long Term Illness)). The feasibility of using propensity scores for the hepatic injury (of course not including possible exposures of interest) to select controls will be tested. The number of cases per control will be chosen on the order of magnitude of the expected odds ratio of the associations. As a first approximation, up to ten controls may be chosen for each case. Analysis will be done using conditional logistic regression, looking for interaction terms between medications. (4)

10.5 COHORT ANALYSIS

For selected at-risk drugs identified in the previous analyses and if events are many enough, incident user cohorts and controls, adjusted or matched on propensity scores will be built, and followed using cox proportional hazards analyses and survival curve functions to analyse the onset of hepatic injury. (14)

11 EXPECTED STRENGTHS AND LIMITATIONS

The methodology relies on proven bases and new initiatives: The case-population methodology is efficient for this type of very rare event with 100% ascertainment rates.
One of the blocking points could be the lack of power in EGB, for which data will be exploit in SNIIRAM.
Another blocking point is the coding errors, for which sensitivity analyses will be performed.
Poor recording of occasional medication (*e.g.* paracetamol) or toxic exposure (*e.g.* alcohol) could be considered as another limitation. In France over 80% of paracetamol use is prescription, and is recorded in the database. It is possible that instances of paracetamol exposure may be missed in non-overdose cases (there is a specific ICD-10 code for liver failure related to drug overdose). There is no reason for that to occur more of less frequently in patients with or without liver injury. Non-differential misclassification of exposure would in fact be conservative for paracetamol. Acute alcoholic liver injury also has a specific ICD

code. This will be included in the sensitivity analyses, to test for interactions for instance between alcohol-related diagnoses and paracetamol for liver injury.

12 EXPECTED RESULTS

From the results of this first study of drug hepatotoxicity in the French national healthcare database, strategies for further explorations will be refined and defined for use in later studies or in a systematic alerting system.

The results of this study could lead to the identification of potentially hepatotoxic agents that have not yet been recognized. This may lead to regulatory intervention, or to changes in the understanding of drug-induced hepatotoxicity. If new hepatotoxic drugs are discovered, this could open the way to translational studies looking at hepatotoxic mechanisms, including genetic predisposition for certain types of hepatotoxic drugs.

The understanding of hepatotoxic risk factors or predisposition will help the regulatory agencies inform users and prescribers of potential risks and risk factors, which would ultimately help the Agency make drugs safer for the end users.

Finally the various sensitivity analysis will help to better understand the methodologies for this kind of study in the national databases, which could result in systematic and routine monitoring of drug-induced hepatotoxicity in the national healthcare system reimbursement database.

Statistical analysis report(s) for case-population study, case-crossover study, case-control study, and cohort study (optional) will be provided.

All results will be published in peer-reviewed journals.

13 REGULATORY ASPECTS

EGB is administered by the French health insurance (*Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés*, CNAMTS) and has been the subject of an agreement with the French commission for data privacy (*Commission Nationale de l'Informatique et des Libertés*; CNIL) (agreements AT/CPZ/SVT/JB/DP/CR05222O of 14 June 2005 and DP/CR071761 of 28 August 2007). A synopsis of the study will be submitted to INSERM two weeks before the start of the study. Authorized and trained personnel will perform data extraction and analysis.

Since the study will be conducted on pre-existing data, it is not necessary to submit it to the Committee for the Protection of Persons for the Southwest and Overseas III (*Comité de Protection des Personnes, Sud-Ouest et Outre Mer III*, CPP– SOOM III).

14 PROJECT DURATION AND STUDY REPORTS

The project duration is 24 months.

Study final report will be established and provided to IReSP together with the financial balance sheet.

15 CONTRACTS

Financing of the study is obtained through IReSP research grant.

16 RESPONSIBILITIES OF THE PARTIES

Financing of the study is obtained through IReSP grant.

The partners in this project have a long history of successfully working together, and have completed a similar but retrospective project, SALT-I.

Department of Pharmacology of the University of Bordeaux (Pharmaco-épidémiologie CIC Bordeaux CIC1401) is the coordinator of the study. It includes 50 permanent professionals supporting the design, implementation, monitoring and publications of pharmacoepidemiological studies. It has just finished a multicentre multi-country of acute liver transplantation (SALT-I), which is the source of this prospective study. The study coordinator, Prof Sinem Ezgi Gülmez, was the scientific director of that previous study. The study team has widespread experience in the management of large publicly or privately funded field studies done at the request of regulatory authorities. The coordinating centre is a member of the European Network of Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance (ENCePP) and works to ENCePP Standards of practice.

This self-supported team includes scientists, study managers, team leaders, CRA, statisticians, data managers, a medical writer and other personnel to a total that varies from 40 to 75 according to its activity. Most of the team has been working in the field and in the centre for more than 5 to 10 years. Personnel on the team are under contract with the university or ADERA, depending on local circumstances and the impossibility for the university to have long-term employment contracts. ADERA, represented by its director, Jean Rivenc, is the non-profit entity managing the personnel that work within INSERM CIC Bordeaux CIC1401, in link with the University of Bordeaux. ADERA is approved by the Ministry of Research and the Rector of Bordeaux. ADERA was also involved in the SALT-I study and provides legal assistance to the project.

The coordinating centre in Bordeaux is the guarantor of the study. It ensures that national and European regulations are respected, as well as Good Pharmacoepidemiology Practices as

described by ISPE (www.pharmacoepi.org) and ENCePP Code of Conduct and methodological standards guide. The study will be registered in the "ENCePP Register of Studies". Study protocol and results will also be made public according to ENCePP requirements.

17 PROVISIONAL STUDY CALENDAR

Study team, regulatory submissions	June – July 2014 (1 month)
Study protocol and statistical analysis plan	September – October 2014 (2 months)
Description of case sets	November – December 2014 (2 months)
Description of control sets	January – February 2015 (2 months)
Description of exposure sets in cases and controls	March – May 2015 (3 months)
Population exposures for drugs of interest	June 2015 (1 month)
Data analysis:	July – August 2015 (2 months)
Extension of the study to SNIIRAM	September 2015 – March 2016 (7 months)
Updated annual version of the Doctoral Study Plan	March 2016
Data analysis:	Early 3rd quarter of 2015 and 1st quarter 2016
Final study report:	August 2016
Individual articles submitted for publication	2015 – 2016
Total duration	**24 months**

These study times are indicative and depend on the numbers of cases identified and the complexity of the exposures for analysis. Some of the task times may overlap. On the other hand, delay to paper acceptance and publication may vary.
Because many of the tasks overlap, it can be estimated that the project can be done within 18 months, even in paper acceptance may be longer.

18 FUTURE AMENDMENTS AND DEVIATIONS

If necessary, any substantial amendment and update to the study protocol after the start of data extraction, including a justification for each amendment or update, dates of each change

and a reference to these sections of the protocol where the change has been made will be prepared. Necessary bodies and ENCePP will be informed without delay.

19 PUBLICATION PLAN

The study will give rise to publications in international peer-reviewed journals.

The papers will be written by the coordinating centre, with the assistance of an in-house medical writer within and beyond the study timeframe. Publications are envisioned concerning study methodology, and study results either globally or per drug family, including methodological issues pertaining to the study.

The authorship and the sequence of authors are to be decided on the basis of the contribution of the members. In case of several publications, author sequence to be decided on by the project group.

20 REFERENCES

1. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study G. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010 Dec;52(6):2065-76. PubMed PMID: 20949552. Epub 2010/10/16. eng.

2. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. Handb Exp Pharmacol. 2010 (196):407-18. PubMed PMID: 20020269. Epub 2009/12/19. eng.

3. Lee WM. Drug-induced hepatotoxicity. N Engl J Med. 2003 Jul 31;349(5):474-85. PubMed PMID: 12890847. Epub 2003/08/02. eng.

4. de Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. British Journal of Clinical Pharmacology. 2004 Jul;58(1):71-80. PubMed PMID: 15206996. Pubmed Central PMCID: 1884531.

5. Gulmez SE, Larrey D, Pageaux GP, Lignot S, Lassalle R, Jove J, et al. Transplantation for Acute Liver Failure in Patients Exposed to NSAIDs or Paracetamol (Acetaminophen): The Multinational Case-Population SALT Study. Drug Saf. 2013 Feb;36(2):135-44. PubMed PMID: 23325533. Pubmed Central PMCID: 3568201. Epub 2013/01/18. eng.

6. Moore N, Gulmez SE, Larrey D, Pageaux GP, Lignot S, Lassalle R, et al. Choice of the denominator in case population studies: event rates for registration for liver transplantation after exposure to NSAIDs in the SALT study in France. Pharmacoepidemiol Drug Saf. 2013 Feb;22(2):160-7. PubMed PMID: 23166053. Epub 2012/11/21. eng.

7. Avillach P, Coloma PM, Gini R, Schuemie M, Mougin F, Dufour JC, et al. Harmonization process for the identification of medical events in eight European healthcare databases: the experience from the EU-ADR project. Journal of the American Medical Informatics Association: JAMIA. 2013 Jan 1;20(1):184-92. PubMed PMID: 22955495. Pubmed Central PMCID: 3555316.

8. Ryan PB, Schuemie MJ, Welebob E, Duke J, Valentine S, Hartzema AG. Defining a reference set to support methodological research in drug safety. Drug Saf. 2013 Oct;36 Suppl 1:S33-47. PubMed PMID: 24166222.

9. Schuemie MJ, Gini R, Coloma PM, Straatman H, Herings RM, Pedersen L, et al. Replication of the OMOP experiment in Europe: evaluating methods for risk identification in electronic health record databases. Drug Saf. 2013 Oct;36 Suppl 1:S159-69. PubMed PMID: 24166232.

10. Theophile H, Laporte JR, Moore N, Martin KL, Begaud B. The case-population study design: an analysis of its application in pharmacovigilance. Drug Saf. 2011 Oct 1;34(10):861-8. PubMed PMID: 21879780. Epub 2011/09/02. eng.

11. Gulmez SE, Larrey D, Pageaux GP, Lignot-Maleyran S, de Vries C, Sturkenboom M, et al. Methodology for a multinational case-population study on liver toxicity risks with NSAIDs: the Study of Acute Liver Transplant (SALT). Eur J Clin Pharmacol. 2013 Mar;69(3):605-16. PubMed PMID: 22878690. Epub 2012/08/11. eng.

12. Lee CH, Wang JD, Chen PC. Case-crossover study of hospitalization for acute hepatitis in Chinese herb users. Journal of Gastroenterology and Hepatology. 2008 Oct;23(10):1549-55. PubMed PMID: 18717756.

13. Lee CH, Wang JD, Chen PC, Health Data Analysis in Taiwan Research G. Case-crossover design: an alternative strategy for detecting drug-induced liver injury. Journal of Clinical Epidemiology. 2012 May;65(5):560-7. PubMed PMID: 22445086.

14. Traversa G, Bianchi C, Da Cas R, Abraha I, Menniti-Ippolito F, Venegoni M. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ. 2003 Jul 5;327(7405):18-22. PubMed PMID: 12842950. Epub 2003/07/05. eng.