



Diana Afonso Domingues

An Application for Orphan Medicinal Product Designation for Mesothelioma Treatment

Monografia realizada no âmbito da unidade de Estágio Curricular do Mestrado Integrado em Ciências Farmacêuticas, orientada pelo Professor Doutor João Nuno Sereno Almeida Moreira e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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Coimbra, 15 de Setembro de 2016.

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List of Abbreviations

COMP – Committee for Orphan Medicinal Products

EMA – European Medicines Agency

EU – European Union

EUCERD – European Union Committee of Experts on Rare Diseases

FDA – Food and Drug Administration

IARC – International Agency for Research on Cancer

MM – Malignant Mesothelioma

OOPD – FDA Office of Orphan Products Development

USA – United States of America

WHO – World Health Organization

1. Abstract

The process of application for orphan drug designation for medicines for rare diseases is regulated by the European Medicines Agency (EMA) in the European Union, and by the Food and Drug Administration (FDA) federal agency in the United States.

This monograph aims at describing the procedural information, criteria and guidance, a medicine must meet to qualify for orphan designation.

The specific case of mesothelioma (a cancer of the mesothelium) will be explored to demonstrate how a medicine can apply for orphan designation. The starting point is the thorough demonstration that this is a rare type of cancer affecting less than 5 in 10 000 people in the European Union, through an extensive research in articles and databases.

The work presented herein will be introduced in the scientific development of TREAT U's pipeline, a company dedicated to the discovery of novel treatments for diseases classified as unmet medical needs in Oncology.

2. Resumo

O pedido de designação de medicamento órfão para uma doença rara é regulado pela Agência Europeia do Medicamento (EMA) na União Europeia, e pela Administração dos Alimentos e Medicamentos (FDA), nos Estados Unidos da América.

A presente monografia pretende descrever os critérios e normas a seguir, bem como a informação necessária reunir para justificar a designação de medicamento órfão.

Neste caso, exploramos o mesotelioma, um tipo de cancro que afecta o mesotélio, e que será a condição para a qual o medicamento que pretende a designação de medicamento órfão será utilizado. O objectivo principal é demonstrar que se trata de um tipo de cancro raro, que afecta menos de 5 pessoas em 10 000, na União Europeia, através de uma extensa pesquisa em artigos e bases de dados.

Este trabalho inseriu-se no desenvolvimento científico de um produto, levado a cabo pela TREAT U, uma empresa dedicada à descoberta de novos tratamentos para doenças oncológicas que não têm respostas terapêuticas adequadas.

Keywords: Rare Disease; Orphan Drug; Mesothelioma; EMA; Application.

3. Introduction

In European Union (EU) countries, any disease affecting less than five people in every 10 000 is considered rare. Rare diseases are often chronic, progressive, degenerative and life-threatening, with a short background of information and scientific knowledge that impairs and delays diagnostics. Patients with rare diseases often find it difficult to access appropriate treatments and care.

Although the number of people with a particular rare disease is small, all rare diseases combined affect millions of people. This is why research on rare diseases is so important and incentives are becoming more frequent. The EU has established several measures to ensure the right to prevention, diagnosis and treatment of rare conditions, promoting the investigation and development of new diagnostic and therapeutic procedures. Otherwise, the interest of industry in research would be scarce because rare diseases represent a small market niche.

The following monograph reports the steps and the procedures to make an application to the Regulatory Authorities (EMA and FDA), to obtain the status of orphan drug for the treatment of a rare disease. This designation will guarantee different benefits to the sponsor, described herein as well.

This work will focus mainly on Part B of the application, which refers to the prevalence of the condition and all the research that must be done and duly justified to prove that the disease affects no more than 5 people in 10 000, in the EU. For this, an extensive review of the literature and reference databases was done, together with a critical presentation of methods, results and conclusions.

4. Rare Diseases

Rare diseases affect a small number of people in the world and often do not have specific treatments available. Moreover, the symptoms can vary greatly from person to person with the same disease, which undermines research and the development of an effective treatment.

In the United States, a disease is rare when affects less than 200 000 people. Rare diseases account for 10% of the American population.

In the European Union, a disease is rare when affects less than 5 people in 10 000. There are 6 to 7 000 rare diseases already discovered and some of them are described in medical literature. Commonly rare diseases have a huge impact on the quality of life of patients, incapacitating them and drastically reducing the average life expectancy.

It is believed that approximately 80% of rare diseases have a genetic component, and 7% of the population of the EU will be affected by a rare disease at some point in their lives. This is a major concern since often these diseases are chronic and life-threatening and there is no effective treatment being developed. Furthermore, approximately 75% of rare diseases affect children, whose quality of life is often compromised by the lack or loss of autonomy, bringing a high level of pain and suffering not only for the patient but also for his/her family. Hence, investigation of the disease is fundamental to develop new treatments, improve diagnostic and empower the patient and the caregivers with information and scientific knowledge about the condition. This, will also have a positive impact at a social level, namely on decreasing discrimination rates and exclusion behaviours.

One of the major hurdles on the development of new treatments for rare diseases, is the lack of investment from the pharma industry, since the market is not as profitable as a non-rare condition. Thus, patients are deprived from access to effective treatment or, when they have it, the price is too expensive.

Rare diseases include rare cancers such as mesothelioma, the cancer that will be discussed in this monograph.

5. Cancer

According to the World Health Organization (WHO), cancer is the uncontrolled growth and spread of cells and it can affect almost any part of the body. Hanahan and Weinberg have described the principles behind the development of cancer, designating ten hallmarks that distinguish cancer cells from normal cells (Hanahan e Weinberg, 2011). One of the common features of cancer is that it often invades surrounding tissue and can metastasize to distant sites. The normal cell turnover becomes unsettled and uncontrolled in the way that cells become more abnormal, old or damaged, ignoring the signals for apoptosis. Tumors are called malignant when they have the ability to invade the surrounding tissues, opposed to benign tumors that do not spread into nearby structures.

4.1. Mesothelioma

Malignant mesothelioma is a rare tumor that affects the cells constituting the mesothelium, which is the membrane that covers and protects various internal organs of the body (lungs, heart and abdominal organs) (Davidson, 2015). This is a rare type of cancer usually diagnosed at a late stage, which makes it highly aggressive, with a reserved prognosis. It has a long latency period of thirty to fifty years, after a possible exposure to carcinogenic agents (Baas *et al.*, 2015). There are three different types of mesothelioma: pleural, pericardial and peritoneal. This work will focus only on malignant pleural mesothelioma, the most common type. Pleura is the serous membrane that bounds lungs and chest cavity.

4.1.1. Causes

For a long time, mesothelioma has been associated with the exposure to asbestos (Rodríguez, 2015). According to Røe and Stella (2015), asbestos consists of a family of natural minerals that has a variety of uses and can be classified in two main families: serpentines that are short, white and curly fibres which include chrysotile; and amphiboles that are straight, blue and long fibres that include amosite, tremolite, actinolite and anthophyllite. Asbestos was classified as class I carcinogen by IARC (International Agency for Research on Cancer) and WHO, which led to the ban of its use and imports in several European countries.

Asbestos was widely used in building materials and for insulation of water and combustion pipes, among other things (Røe e Stella, 2015).

Approximately 70 to 90% of mesothelioma cases are related to exposure to asbestos (Maloney, Smith e Rose, 2002). Epidemiological studies show that mesothelioma is most common in men, which is probably related to women being less exposed in a labour context.

4.1.2. Symptoms

Symptoms of mesothelioma vary according to the location, type and stage of the cancer.

At the beginning of the disease, most people have no symptoms and it is difficult to detect the tumor on X-ray examination. The most frequent symptoms are pleural effusion, dyspnoea, chest pain and chronic cough (Krug *et al.*, 2015). Later, dysphagia can occur and pain becomes worse and persistent. People may also have general symptoms like fever, weakness, night sweats and unexplained weight loss.

Symptoms of mesothelioma may not appear until up to 30 to 50 years after initial exposure to asbestos. Thus, it is estimated that the peak of incidence in Europe will be around 2020. Only countries that have regularized the use of asbestos in the 70's are not currently having an increase in the number of diagnosed cases (International *et al.*, 2014).

4.1.3. Diagnosis

The diagnosis can be done using different tools. The most frequently used are the chest X-ray, which can provide information about the presence of effusion, diffuse pleural thickening or masses; computed tomography (CT); positron emission tomography (PET) and magnetic resonance imaging (MRI) (Borghaei *et al.*, 2012). There are other methods, such as pleural fluid cytology and the thoracentesis which evaluate the hyaluronic acid levels (Rodríguez, 2015). If these levels are high, there is a chance of malignant pleural mesothelioma.

For a reliable diagnosis these exams are always accompanied by laboratory blood tests, and it is important to have tissue biopsy and to use the correct immunohistochemistry.

4.1.4. Treatment

Unfortunately, the prognosis for mesothelioma is poor and the incidence will increase up to an expected peak of cases by 2020. Malignant mesothelioma is an aggressive tumor and in most cases the diagnosis is made too late, when the tumor is too advanced, making a multimodality treatment impossible to apply and precluding the possibility of surgically resection (Ak *et al.*, 2015).

Currently, treatments are mainly intended to reduce and mitigate the symptoms and to increase survival. One of the symptoms that decrease quality of life is pleural effusion. Some options for reducing dyspnoea and chest pain are chest tube drainage, insertion of an indwelling pleural catheter or thoracoscopy.

In cases where surgery is not an option at all, the preferred treatment is platinum-based chemotherapy or a combination of cisplatin and gemcitabine as second line treatments (Ak *et al.*, 2015). In these cases, the treatment is only palliative, that is, it only relieves symptoms and improves life expectancy. The National Institute for Health and Clinical Excellence, recommends as first-line, the treatment with cisplatin and pemetrexed, or in occasional situations, cisplatin can be replaced by carboplatin (Infirmary e Oncologist, 2015). The treatment with cisplatin and pemetrexed is usually done with four to six cycles, depending on patient response and toxicity. However, pemetrexed is very expensive and requires

additional care supplementation of acid folic and vitamin B12, to avoid pemetrexed toxicity (Ak *et al.*, 2015). Some patients cannot take pemetrexed, so there is a second-line option that consists in a combination of cisplatin and gemcitabine (Borghaei *et al.*, 2012). There are also few small phase-III studies with a reduced number of patients using vinorelbine; benefits occur when it is used in combination with another agent, but further studies are needed (Infirmary e Oncologist, 2015). The platinum-based chemotherapy seems to be the most effective therapy for advanced stages of the disease (Ak *et al.*, 2015).

Another option is radiotherapy, which can be used in palliative care (to reduce symptoms), as an adjuvant in a multimodality treatment, or in prevention regimens (Baas *et al.*, 2015). Often, the candidates for surgery are treated with surgery followed by adjuvant chemotherapy and radiotherapy (Borghaei *et al.*, 2012).

Surgery is mostly used for staging procedures or with palliative or curative intent. Surgery allows the examination of the tumor and the draining of the pleural effusion. The aim of this procedure is to resect as much visible tumour as possible, using different surgical procedures.

The median survival can vary from 1-2 years with treatment. This is the main reason why continuous research of the condition and more effective treatments for patients with mesothelioma are still required (Ak *et al.*, 2015).

6. Orphan Medicinal Products

5.1. EMA

According to the European Medicines Agency, the Orphan designation is used for products intended for the diagnosis, prevention or treatment of rare diseases, which are life-threatening, seriously debilitating or chronic. This can also be applied when there is no satisfactory method of diagnosis, prevention or treatment authorised in the Community, or if it exists, is less effective than the new one.

EMA has a specific committee, the Committee for Orphan Medicinal Products (COMP), constituted by people nominated by the EU member states, which have the responsibility of reviewing all applications from the pharmaceutical industry to have an “orphan-medicinal-product designation”. They also establish the rules for orphan products in the EU, define the procedures for making the request for the designation and set the guidelines.

The interest of the pharmaceutical industry in developing drugs for a rare disease is limited owing to the requirements for a large investment in research and development for a product that will have a very small target population. For this reason, in the EU there is a specific legislation, the Regulation (EC) No 141/2000 of the European Parliament, that incentivises the pharmaceutical industry to develop orphan medicinal products, namely:

- Market exclusivity for 10 years in the EU after the approval of the marketing authorisation;
- Access to the centralised authorisation procedure;
- Scientific advice from EMA to optimise the development of a dossier with all the regulatory requirements of this agency;
- Grants and fee reductions for different activities guaranteed by the European Commission with the support of the European Parliament.

The market exclusivity can be reduced to six years, if at the end of the fifth year the prevalence of the disease changes.

Since 1983, more than 2 200 rare disease treatments have entered the research pipeline, but only 360 have been approved for marketing.

To request the orphan designation, the sponsor must demonstrate in the first place that the addressed condition is rare. EMA requires a wide search in databases, papers of clinical trials, and review of the literature to demonstrate the prevalence and incidence of the disease. This document must describe all methods applied in the search, results obtained and conclusions withdrawn.

The sponsor must also justify that without incentives, marketing the medicinal product in EU would not generate sufficient return on investment.

According to EMA, the application should start with the sponsor's name and address, description of active ingredients of the product, proposed therapeutic indication and a justification for the request. This document must focus on the problem statement and key definitions, identification of epidemiological data, validity and comparability of data, combined data from different studies and a report discrimination of all costs associated with the product development and marketing, as well as the expected costs for after the submission of the application.

The sponsor has also to demonstrate that there are no other viable and effective options, or if they exist, the sponsor should demonstrate significant benefit of its product.

The application for orphan product designation can be made in any stage of the product development. However, it should always be done before the market authorization. The only exception is the case of a product already authorized in the market and for which the sponsor wants a new therapeutic indication in a rare disease.

EMA asks for one original application form, signed and dated, including full copies of bibliographical references and two copies of the application in electronic form. The application should regard the form and table of contents provided in the Annex of the guideline of 9 July 2007.

5.1.1. The Application

The application is divided in sections and each section should be based in relevant scientific literature.

A. Description of the Condition

- Name of the active substance, by its International Non-proprietary Name or a common name if non-existent;
- Proposed indication and ATC code;
- Proposed details of the medicinal product, when available, such as pharmaceutical form and route of administration;
- Name and permanent address of the sponsor and contact person, taking into account that the sponsor must be established in the Community and can be an individual or a company;
- The name of the manufacturer of the active substance and medicinal product;
- Description of the condition, including the details of the condition based on published references or textbooks, the proposed orphan indication, medical plausibility including a brief explanation of the mechanism of action, and the justification of the life-threatening or debilitating nature of the condition.

B. Prevalence of the Condition

Prevalence of the condition must be specified in accordance with the requirements of the Commission Regulation No 847/2000. Prevalence is defined as the number of persons affected by the condition in the EU, at the time the application is made. The prevalence ratio is made between the number of people who have the disease at the time the application is made, and the reference population. To calculate the prevalence, the sponsor must do an extensive research and should include a comprehensive review of authoritative references. It is important to include the largest number of member states as possible, and the final result should always be calculated for 10 000 people in EU. The sponsor must clearly indicate how he came to the result, indicating all data and references used, as well as information contained in databases on rare diseases. In case of extrapolating data, the applied methodology has to be justified.

For some diseases, calculating their prevalence is the hardest part. When the disease has a short duration, the sponsor is advised to calculate the incidence instead of prevalence.

C. Potential for return on investment

Documentation shall also specify all costs that the sponsor expects to incur during the research and product development, and should be referred any grants, tax incentives or other cost recovery provisions received. Lastly, the sponsor should also state the estimated revenue from the sale of the product, for 10 years.

D. Other methods for diagnosis, prevention or treatment of the condition

At this part, the sponsor should clarify that there are no alternative diagnostic, prevention or treatment procedures, satisfying the patient's needs, or when existent, the sponsor has to prove the clinical superiority, reviewing the existing methods and products.

E. Description of the stage of development

This part requires an indication of the stage of development of the product.

F. Bibliography

The main sources of information are articles from peer-reviewed journals, databases and registries, which will form the basis of a systematic review that will provide credible information. All obtained information can be compiled in a table format.

If the product is intended for more than one indication, the sponsor must submit one application for each indication. As an example, prevention and treatment are different indications.

The sponsor will receive an answer from the Committee within 90 days after the reception of a valid application and the committee has the right to ask for more evidence.

According to the Regulation (EC) No 141/2000, the application can be reviewed at the time of market exclusivity revision. This analysis includes comparative results of conducted studies, a literature review, marketing studies and surveys of patients.

5.2. FDA

FDA has also a department for the regulation of products that evaluates requests for the development of new products - the FDA Office of Orphan Products Development (OOPD). The main role of OOPD is to make the scientific assessment and validation of the clinical data, to rationally decide which applications will move forward. This Office gives support to diverse medical departments, patients' associations and other organizations.

As it happens in Europe, the United States grant incentives to the pharmaceutical industry for the development of products that can be used in rare diseases.

A product can only be candidate for orphan drug designation if the sponsor demonstrates that the disease for which it will be used affects less than 200 000 people in the United States.

The incentives assured by the FDA are divided into formal (market exclusivity, tax credits, Prescription Drug User Fee Act (PDUFA) fee exemption and grants), and informal (assurance of venture capital and the involvement of OOPD).

5.2.1. The Application

The guideline 21 CFR 316.20 and 21 CFR 316.21 defines the designation of orphan product and the rules for the application to orphan drug designation. The submission form must contain the following topics:

- Name and address of the sponsor, and person of contact;
- Statement of the request;

- Generic name and brand name of the product, as well as the physical and chemical properties and description of the formulation;
- Proposed dose and route of administration;
- Valid scientific information specifying the condition for which the sponsor is requesting the designation of orphan drug and justifying the benefits in patient's quality of life;
- Current regulatory and marketing status;
- Prevalence of the condition in United States, confirming that is a rare condition that affects less than 200 000 people. This justifies that in absence of incentives, research and development of such products is not compensatory;
- Summary analyses of pharmacological effects of the product;
- Analyses of the clinical and non-clinical data of the product and the disease, including published articles;
- Definition of the population to be used in future clinical trials;
- Security and Efficacy data (such as data of clinical trials, case reports or data from animal models or in vitro studies);
- Data from non-clinical studies and laboratorial data.

The application should be sent in duplicates with a cover letter signed or in digital format, to the FDA Office of Orphan Products Development. The sponsor will receive a letter confirming the reception of the application and an answer with the decision within 90 days. In case of a negative answer, the sponsor can resort.

The application for orphan designation can be made for a completely new product developed for that specific condition or it can be based on an existing product, with evidence of clinical superiority in that rare disease.

7. Orphanet

Orphanet is one of the most important portals with information on rare diseases and orphan drugs in Europe. It provides direct online access to all stakeholders, with an inventory of rare diseases and an encyclopaedia in 6 languages. It also lists all ongoing

national and European-level funded research projects to facilitate the research, and features a list of patient's organizations. Lastly, this database also includes a list of authorized orphan products used to treat rare diseases in Europe.

8. Research for Calculating the Prevalence

7.1. Research on Pubmed

The work developed for this monograph relied on a vast research in articles using the Pubmed, a free full-text archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health's National Library of Medicine. The main goal was to make a review of scientific articles to obtain data on the prevalence of mesothelioma in several EU countries. The main sources of information were medical/scientific literature, cancer databases and rare diseases databases.

In order to search for relevant articles, we extended the research to include the terms “mesothelioma” and “epidemiology” in the title of articles related to Europe. The final mesh terms with which the survey was conducted, were “Mesothelioma[Title] AND Epidemiology[Title] AND Europe[Mesh Terms]”, thus obtaining a total of 204 articles.

Each article was appraised in four criteria:

- Epidemiological data (prevalence, incidence, mortality, survival)
- Geographical scope
- Condition
- Date of data collection

When necessary, the entire article was reviewed. According to the available information, the articles were classified in three different categories, as described in table I.

Table I. Classification of the literature.

Class	Classification	Epidemiological Data	Geographical Scope	Condition
<u>A</u>	Perfectly Adequate	Prevalence OR (incidence AND mean survival time)	Every EU member states + Iceland, Liechtenstein and Norway	Mesothelioma
<u>B</u>	Adequate	Prevalence OR Incidence	One or more	Mesothelioma or Malignant Pleural Mesothelioma
<u>C</u>	Inadequate	One or more criteria were not met		

EU member states are: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Ireland, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Spain, Slovakia, Slovenia, Sweden and the United Kingdom.

The information obtained was summarized in a table containing all 204 articles. Table II contents demonstrate the evaluated criteria for calculating the prevalence of mesothelioma in EU member states (for space restrictions, only the first 6 cases are presented as an example. The entire research is detailed in Annex I).

Table II. Analysis of references for adequacy assessment.

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
1	Zocheti. Med Lav. 2015 Nov 22;106(6):431-46.	Peer-reviewed journal	Italy		mesothelioma and lung cancer							C
2	Magnani et al. Med Lav. 2015 Sep 9;106(5):325-32	Peer-reviewed journal	Italy	2011	Pleural mesothelioma	Data from the 'Epidemiology, Public Health and Occupational Medicine' section of the III Italian Consensus Conference on Pleural	Consensus conference report		3.64 per 100,000 person/years in men and 1.32 in women			B
3	Boulangier et al. Occup Environ Med. 2015 Nov;72(11):792-7	Peer-reviewed journal		1978-2009	Digestive cancers							C
4	Jarvholm et al. Scand J Public Health. 2015 Dec;43(8):875-81.	Peer-reviewed journal	Sweden	1995-2012	malignant pleural mesothelioma	Cases identified in Swedish Cancer Registry and restricted to persons born in Sweden.	evaluate how the ban has influenced age-specific mortality rates over time, and to conduct a health impact assessment on burden of mesothelioma death avoided by this ban up to 2012.					C
5	Petrucci et al. Ann Ig. 2015 May-Jun;27(3):526-32.	Peer-reviewed journal	Italy (Umbria)	2003-2013	Malignant Mesothelioma	Cases of MM reported to Umbrian Population Cancer Registry			191 (156 males)			C
6	Marinaccio et al. Occup Environ Med. 2015 Sep;72(9):648-655	Peer-reviewed journal	Italy	1993-2008	Pleural mesothelioma	Data collected by the Operating Regional Center (COR), National Register of Mesotheliomas	surveillance system		3.84 /100,000 for men and 1.45 /100,000 for women (In 2008) Total 15,845 mesothelioma cases (1993-2008)			B

The results of the reference review and adequacy assessment were presented according to the format suggested by the Committee for Orphan Medical Products (COMP) on "Points to Consider on the calculation and reporting of prevalence of a condition for orphan designation" (COMP/436/01).

On the combined articles of the final search, which resulted in 204 references:

- 0 references were classified as A;
- 19 were classified as B;
- 185 were classified as C.

Among the references classified as B, none presented prevalence data. Italy was the country with the highest incidence, with 0.576/10,000 in regions with higher levels of asbestos exposures, and Denmark with the lowest rate of 0.053/10,000, followed by Germany and France with 0.08/10,000. Overall survival ranged from 9.3 months (Norway, 2009) to 18 months (Germany, 2011) and mean survival time was 13 months (See estimation of prevalence based on references described in Annex 2).

One study, classified as C for data collection in 1995-2002, registered an incidence of 0.19/10,000 and a prevalence of 0.24/10,000 in Europe (Siesling *et al.*, 2012).

Therefore, it was only possible to infer on the prevalence for mesothelioma from 8 retrieved references, with estimation clearly below 5/10,000. The highest prevalence was estimated for the United Kingdom (0.55/10,000). Hence, it is safe to assume that malignant mesothelioma affects no more than 0.55/10,000 in the European community.

7.2. Research on Databases

The most relevant databases on orphan diseases are Orphanet and RARECARE. The main results from the conducted research are the following:

- Orphanet: The number obtained from this database in "Prevalence and incidence of rare diseases: Bibliographic data, Number 1, March 2016: Prevalence, incidence or number of published cases listed by "Prevalence, incidence or number of published cases listed by diseases (in alphabetical order)", is 0.31 in 10,000 for prevalence and 0.19 in 10,000 for incidence;

- RARECARE: This database provides a list of rare diseases, including malignant mesothelioma. The incidence data from February 2011 is 0.19/10,000 (15,263 cases).

In conclusion, and considering all limitations from the available information, the collected data shows that the prevalence is clearly below the threshold for orphan designation (5/10,000). According to our research, it is reasonable to estimate that malignant mesothelioma affects no more than 0.55/10,000 in the European Community.

9. Conclusion

The extensive research developed within the context of this monograph was intended to be part of an application for an orphan drug designation for a new medicine for the treatment of mesothelioma.

The wide-range review made it possible to achieve the initial goal: to prove that the prevalence of mesothelioma is clearly below the threshold set for the European Union (5 / 10,000), thus proving that it is a rare disease. Moreover, it was demonstrated that mesothelioma has no effective treatments, and is therefore a disease that needs more research and development to ensure a more effective response from patients.

The peak of the disease will likely be verified by 2020. Hence, it is necessary to invest in this area in an attempt to close gaps and enable new treatments that can prolong and improve the life of patients who will suffer from this type of cancer.

Although I was aware of the difficulties faced by cancer patients, I learned from this work the particular reality of rare diseases. There is an urgent need for more precise tools for diagnosis and effective treatments, which would benefit from a more comprehensive study of the disease. EU and USA have developed incentives to research and development on rare diseases to ensure that every human being has equal rights in regard to their health, surpassing the lack of market interest from big pharmaceutical industries.

Throughout this work I have acquired knowledge on the process of application for orphan designation to EMA, and how the agencies of medicine act (including EMA and FDA), in the field of rare diseases.

Finally, I had the opportunity to work directly with a spin-off from the University of Coimbra that is dedicated to the research and development of a very promising nanomedicine, with application in a rare disease. I saw the effort and commitment that a whole team dedicate when embracing a project of this nature, which was very rewarding. It was my first contact with an entrepreneurial environment.

Overall, this was a project that required time and dedication but the end result made me very proud and happy to contribute to a process that could lead to the approval of a new drug for the treatment of mesothelioma.

10. References

Scientific Articles

- AK, G. *et al.* - The effectiveness and safety of platinum-based pemetrexed and platinum-based gemcitabine treatment in patients with malignant pleural mesothelioma. **BMC cancer**. . ISSN 1471-2407. 15:2015) 510. doi: 10.1186/s12885-015-1519-z.
- BAAS, P. *et al.* - Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. **Annals of oncology: official journal of the European Society for Medical Oncology / ESMO**. . ISSN 1569-8041. 26 Suppl 5:July (2015) v31–9. doi: 10.1093/annonc/mdv199.
- BORGHAEI, H. *et al.* - Malignant Pleural Mesothelioma Clinical Practice Guidelines in Oncology. 10:1 (2012) 26–41.
- DAVIDSON, B. - Prognostic factors in malignant pleural mesothelioma. **Human pathology**. . ISSN 1532-8392. 46:6 (2015) 789–804. doi: 10.1016/j.humpath.2015.02.006.
- HANAHAN, D.; WEINBERG, R. A. - Review Hallmarks of Cancer : The Next Generation. **Cell**. . ISSN 0092-8674. 144:5 (2011) 646–674. doi: 10.1016/j.cell.2011.02.013.
- INFIRMARY, B. R.; ONCOLOGIST, C. M. - Medical and oncological management of malignant mesothelioma. **British Journal of Hospital Medicine**. 76:7 (2015) 384–389.
- INTERNATIONAL, T. *et al.* - Past trends and future prediction of mesothelioma incidence in an industrialized area of Italy , the Veneto Region. **Cancer Epidemiology**. . ISSN 1877-7821. 38:5 (2014) 496–503. doi: 10.1016/j.canep.2014.08.007.
- KRUG, L. M. *et al.* - Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): A phase 3, double-blind, randomised, placebo-controlled trial. **The Lancet Oncology**. . ISSN 14745488. 16:4 (2015) 447–456. doi: 10.1016/S1470-2045(15)70056-2.
- MALONEY, D. G.; SMITH, B.; ROSE, A. - Rituximab: Mechanism of action and resistance. **Seminars in Oncology**. . ISSN 00937754. 29:1 SUPPL. 2 (2002) 2–9. doi: 10.1053/sonc.2002.30227.
- RODRÍGUEZ, F. - Diagnosis and Treatment of Malignant Pleural Mesothelioma &. **Archivos de Bronconeumologia**. 51:4 (2015) 177–184.
- RØE, O. D.; STELLA, G. M. - Malignant pleural mesothelioma: history, controversy and future of a manmade epidemic. **European respiratory review: an official journal of the European Respiratory Society**. . ISSN 1600-0617. 24:135 (2015) 115–31. doi: 10.1183/09059180.00007014.

International Guidelines and Recommendations

COMMISSION REGULATION (EC) No 847/2000 of 27 April 2000, available on Internet:
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf

ENTR/6283/00 Revision 4 - Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another, 9 July 2007, available on Internet:
http://ec.europa.eu/health/files/orphanmp/doc/orphan_form_3013/ec_guideline_rev_4_12_06_2013_en.pdf

Guidance 21/PART 316—Orphan Drugs – 12 June 2013 – FDA. [Accessed on 02/06/16]. Available on Internet: <http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=91b7be5e87481538e33a4c0a76ba7183&n=21y5.0.1.1.6&r=PART&ty=HTML>

Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products – Rev. 3 from 2005 EMA, available on Internet:

http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation - COMP/436/01 – 26 March 2002 – EMA, available on Internet:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003773.pdf

Procedure for Orphan Medicinal Product Designation – Guidance 710915/2009 – Rev. 13 from 22 June 2015 - EMA, available on Internet:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003769.pdf

Rare Diseases: Common Issues in Drug Development Guidance for Industry - DRAFT GUIDANCE – August 2015 from FDA, available on Internet:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf>

REGULATION (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, available on Internet:
<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>

Databases

European Commission website – [Accessed on 18/06/2016]. Available on Internet: http://ec.europa.eu/health/human-use/orphan-medicines/index_en.htm

European Medicines Agency - Medicines for Rare Diseases – [Accessed on 3/05/2016]. Available on Internet: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp&mid=WC0b01ac058002d4eb

Global Genes website – [Accessed on 18/06/2016]. Available on Internet: <https://globalgenes.org/rare-diseases-facts-statistics/>

National Cancer Institute website – [Accessed on 18/06/2016]. Available on Internet: <http://www.cancer.gov/about-cancer/understanding/what-is-cancer>

National Organization for Rare Disorders (NORD) website – [Accessed on 11/03/2016]. Available on Internet: <http://rarediseases.org/rare-diseases/mesothelioma/>

Orphan Drug Designation – 1 March 2012 – FDA. [Accessed on 04/06/16]. Available on Internet: <http://www.fda.gov/downloads/forindustry/developingproductsforrarediseasesconditions/oodnewsarchive/ucm294786.pdf>

Orphanet website – [Accessed on 24/04/2016]. Available on Internet: http://www.orpha.net/consor/cgibin/Education_AboutRareDiseases.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTRAREDISEASES

Rare Disease UK (RDUK) website – [Accessed on 18/06/2016]. Available on Internet: <http://www.raredisease.org.uk/about-rare-diseases.htm>

World Health Organization (WHO) website – [Accessed on 24/05/16]. Available on Internet: <http://www.who.int/en/>

Appendix

Annex I. Analysis of references for adequacy assessment

Data collected on Final PubMed search, according to the terms "Mesothelioma/epidemiology[mh:noexp] AND Europe[MeSh Terms] AND ("2006/01/01"[PDat] : "2016/04/20"[PDat]) OR (Mesothelioma[Title] AND Epidemiology[Title] AND Europe[Mesh Terms])"

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
1	Zocheti. Med Lav. 2015 Nov 22;106(6):431-46.	Peer-reviewed journal	Italy		mesothelioma and lung cancer							C
2	Magnani et al. Med Lav. 2015 Sep 9;106(5):32532	Peer-reviewed journal	Italy	2011	Pleural mesothelioma	Data from the 'Epidemiology, Public Health and Occupational Medicine' section of the III Italian Consensus Conference on Pleural	Consensus conference report		3.64 per 100,000 person/years in men and 1.32 in women			B
3	Boulanger et al. Occup Environ Med. 2015 Nov;72(11):792-7	Peer-reviewed journal		1978-2009	Digestive cancers							C
4	Jarvholm et al. Scand J Public Health. 2015 Dec;43(8):875-81.	Peer-reviewed journal	Sweden	1995-2012	malignant pleural mesothelioma	Cases identified in Swedish Cancer Registry and restricted to persons born in Sweden.	evaluate how the ban has influenced age-specific mortality rates over time, and to conduct a health impact assessment on burden of mesothelioma death avoided by this ban up to 2012.					C
5	Petrucci et al. Ann Ig. 2015 May-Jun;27(3):526-32.	Peer-reviewed journal	Italy (Umbria)	2003-2013	Malignant Mesothelioma	Cases of MM reported to Umbrian Population Cancer Registry			191 (156 males)			C
6	Marinaccio et al. Occup Environ Med. 2015 Sep;72(9):648-655.	Peer-reviewed journal	Italy	1993-2008	Pleural mesothelioma	Data collected by the Operating Regional Center (COR), National Register of Mesotheliomas	surveillance system		3.84 /100,000 for men and 1.45 /100,000 for women (in 2008) Total 15,845 mesothelioma cases (1993-2008)			B

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
7	Beckett et al. 2015 Lung Cancer. 2015 Jun;88(3):344-8	Peer-reviewed journal	UK (England and Wales)	2008-2012	Malignant pleural mesothelioma (MPM)	Data collected for the UK National Lung Cancer Audit	Cohort		8740 cases submitted to the audit [England : (2008: 1310; 2009:1688; 2010: 1717 cases; 2011: 1735 cases; 2012: 1885 cases) Wales: (2008: 86; 2009: 67; 2010: 91 cases; 2011:82 cases; 2012: 79	Overall median survival was 9.5 months, with a 1YS of 41.4% and 3YS of 12.0%. Median survival increased from of 9.2 months in 2008 to 10.5 months in 2012		B
8	Doyen et al. Cancer Radiother. 2015 May;19(3):211-9; quiz 231-2, 235.	Peer-reviewed journal			Proton beam therapy	Systematic review on Medline with the keywords: proton beam therapy, cancer, heavy particle, charged particle.						C
9	Lorkowski et al. Adv Exp Med Biol. 2015;852:5-10	Peer-reviewed journal	Poland	2006-2012	malignant pleural mesothelioma.	retrospective analysis of the patients' medical records	shoulder pain as a rare, first symptom of pleural mesothelioma					C
10	Binazzi et al. G Ital Med Lav Ergon. 2014 Oct-Dec;36(4):360-4	Peer-reviewed journal	Italy									C
11	Jarvholm et al. J Occup Environ Med. 2014 Dec;56(12):1297-301.	Peer-reviewed journal	Sweden	1971 - 1993	Pleural mesothelioma	Swedish Cancer Registry	Cohort of workers in the Swedish construction industry (n=389,132		406 cases			C
12	Hajok et al. ScientificWorldJournal. 2014;2014:284072	Peer-reviewed journal	Poland		asbestos-related lung cancers							C
13	Simonsen et al. Int J Tuberc Lung Dis. 2014 Oct;18(10):1211-9.	Peer-reviewed journal	Denmark		risk of cancer in patients with active tuberculosis (TB							C
14	Girardi et al. Cancer Epidemiol. 2014 Oct;38(5):496-503.	Peer-reviewed journal	Italy (Veneto Region)	1987-2010	Malignant Pleural Mesothelioma	Regional Mesothelioma Registry	Enquiries are made at all the hospital departments involved	4.5 million of inhabitants, reference year: 2001	1600 new cases			C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
15	Langhoff et al. Dan Med J. 2014 Sep;61(9):A4902.	Medical journal	Denmark (Northern Jutland)	1996 to 2012	Malignant Mesothelioma of the pleura		Retrospective study in women with MM of the pleura	Female population is 288,369	30 cases (0.53/100,000 person years in women)	Mortality 0.0057% Median survival 12 months Women: 1-year survival of 58%; 5-year survival 58%		B
16	Lauk et al. Ann Thorac Surg. 2014 Nov;98(5):1748-54	Peer-reviewed journal			Malignant pleural mesothelioma MPM	perioperative outcome in 251 consecutively treated patients at three high-volume mesothelioma	retrospective study					C
17	Varivonchik. Med Tr Prom Ekol. 2014;(1):18-22	Peer-reviewed journal	Ukrain	2001-2011	Malignant Mesothelioma of the pleura				240.5 +/-29.0			C
18	Ballan et al. Ann Ist Super Sanita. 2014;50(2):133-8	Peer-reviewed journal	Italy (Biancavilla, Province of Catania, Sicily)	1988-1992	effect of fibrous amphiboles		in vitro and in vivo studies					C
19	Bruno et al. Ann Ist Super Sanita. 2014;50(2):111-8.	Peer-reviewed journal	Italy (Biancavilla, Sicily)	1998 - 2011	malignant mesothelioma	collected by Local Health Unit physicians according to Sicilian Operative Regional Centre (COR) of the National Mesothelioma Registry (ReNaM)	Standardized procedures, questionnaires and classifications.		28 cases (1998-2011) overall Standardized Incidence Ratio (SIR) was 5.76 (95% CI 3.76-8.44) respectively, 3.69 (95% CI 1.97-6.32) in men and 13.08 (95% CI 6.97-22.00) in women.			B
20	Reid et al. Thorax. 2014 Sep;69(9):843-50.	Peer-reviewed journal	5 cohorts from Italy and 1 from Australia	? - 2008	mesothelioma	data from 6 cohort studies of exposed workers and 2 cohorts with residential exposure	case control design	22 048 people with asbestos exposure	707 cases of pleural MM and 155 cases of peritoneal MM			C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
21	Khan et al. Lung Cancer. 2014 Jul;85(1):99-100.	Peer-reviewed journal	United Kingdom	2012	Stage distribution and performance status of newly diagnosed patients in a UK regional mesothelioma centre.	patients referred to the Medical Oncology Department at the University Hospital South Manchester (UHSM)	retrospective study to assess the stage distribution and performance status					C
22	Boffetta et al. Crit Rev Toxicol. 2014 May;44(5):436-49	Peer-reviewed journal			mesothelioma	systematic review of epidemiological studies on the risk of mesothelioma among workers exposed to SVF, and toxicological studies on SVF and mesothelioma						C
23	Ascoli et al. Cancer Epidemiol. 2014 Jun;38(3):273-8.	Peer-reviewed journal	Italy (Lazio region)	2001-2012	mesothelioma	mesothelioma registry from central Italy of the National Mesothelioma Register network (ReNaM) as well as a pathology-	Population-based study	5.5 million inhabitants	791 cases			B
24	Lacourt et al. Thorax. 2014 Jun;69(6):532-9.	Peer-reviewed journal	France	1998 - 2002	Pleural Mesothelioma	population-based case-control study	cases that can be attributed to asbestos exposure					C
25	Jennings et al. Cancer Epidemiol. 2014 Feb;38(1):35-41.	Peer-reviewed journal	Republic of Ireland	1994-2009	Malignant pleural mesothelioma	cases reported since the establishment of the National Cancer Registry of Ireland (NCRI)	Cohort	using the European standard population	337 cases (18.2 cases per million (cpm) per year)	Survival: 197 days in males and 253 days in females		B
26	Offermans et al. J Occup Environ Med. 2014 Jan;56(1):6-19.	Peer-reviewed journal	Netherlands		Occupational asbestos exposure and risk of pleural mesothelioma, lung cancer, and laryngeal		Prospective cohort study (58,279 men, aged 55 to 69 years)		132 cases (in 17,3 years)			C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
27	Campbell et al. Bull Cancer. 2013 Dec;100(12):1283-93.	Peer-reviewed journal	France		Malignant pleural mesothelioma (MPM)		review			median survival 12,7 months to 17,7 (treated with pemetrexed/platinum)		C
28	Goodman et al. Regul Toxicol Pharmacol. 2014 Feb;68(1):8-15	Peer-reviewed journal			risk of mesothelioma and lung cancer in electricians due to asbestos exposure		critical review					C
29	Mastrangelo G et al. Med Lav. 2013 Sep-Oct;104(5):351-8	Peer-reviewed journal	Italy (Veneto region)	2000-2011	health surveillance on carcinogens, including asbestos							C
30	Järnholm et al. Am J Ind Med. 2014 Jan;57(1):49-55	Periodical Journal	Sweden	1972-2009	Pleural Mesothelioma	cohort of construction workers, prospectively followed after participation in health surveillance	Cohort	389,132 men	419 cases			C
31	Frost. Br J Cancer. 2013 Oct 1; 109(7): 1965-1973	Peer-reviewed journal	Great Britain	1971-2005	Mesothelioma	analysis of members of the cohort who died with mesothelioma	Prospective cohort of asbestos workers in GB (n=98,912)			647		C
32	Serrier et al. Eur J Health Econ. 2014 Jul;15(6):661-73	Peer-reviewed journal	France		respiratory cancers							C
33	Camiade et al. Am J Ind Med. 2013 Nov;56(11):1307-16	Peer-reviewed journal	France	1998-2009	mesothelioma	exhaustive recording in French National Mesothelioma Surveillance Program						C
34	Rosell-Murphy et al. BMC Public Health. 2013; 13: 723	Peer-reviewed journal	Spain (Barcelona)	2011 - 2013	Mesothelioma	Hospital Parc Tullí (5 towns in Barcelona) through Primary Health Care Teams	matched case-control study with follow-up of both cohorts	174,515	17/year 51 in the 3 years			B
35	Budroni et al. Ann Ital Chir. 2014 MayJun;85(3):244-8.	Peer-reviewed journal	Italy (Sassari)	1992-2010					70 cases males: 1.2/100,000 females: 0.3/100,000	males: 0.6/100,000 females: 0.2/100,000		B

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
36	Magnani et al. Med Lav. 2013 May-Jun;104(3):191-202	Peer-reviewed journal	Italy		MPM		Consensus development conference					C
37	Berra. G Ital Med Lav Ergon. 2013 Jan-Mar;35(1):61-2	Peer-reviewed journal	Italy				Letter to editor					C
38	Romeo al. Med Lav. 2013 Mar-Apr;104(2):115-25	Peer-reviewed journal	Italy (Lazio Region)	2001-2009	Malignant Mesothelioma	Results of the activities of the regional register			600 cases 1.8 in men and 0.5 in women per 100,000 inhabitants			B
39	Ried et al. Chirurg. 2013 Nov;84(11):987-93	Peer-reviewed journal	Germany (Regensburg)	January 1998 - August 2011	MPM	cases reported to the tumor centre Regensburg	Retrospective analysis		0.8/100,000 inhabitants	overall median survival 14-18 months (1-year survival rate 62 %, 3-year survival rate 15 %)		B
40	Tarrés et al. Occup Environ Med. 2013 Aug;70(8):588-90	Peer-reviewed journal	Spain (Barcelona)	2000-2009	Pleural mesothelioma	medical records of patients diagnosed with pleural mesothelioma between 2000 and 2009	Retrospective cohort study	2005 population as an estimation of the mean population between 2000 and 2009	24 cases			C
41	Chellini E et al. Epidemiol Prev. 2013 Jan-Feb;37(1):43-50	Peer-reviewed journal	Italy (Tuscany)	1988-2009	Pleural mesothelioma	records of Tuscan Operating Centre of the Italian registry				Mortality/incidence ratio closer to 1.		C
42	Binazzi A et al. Epidemiol Prev. 2013 Jan-Feb;37(1):35-42	Peer-reviewed journal	Italy	1993-2008	Malignant mesothelioma	Regional Operating Centre records in ReNaM	Descriptive analysis of MM cases and environmental exposure		15,845 cases; 12,065 related to exposure			C
43	De Zotti R et al. Med Lav. 2013 Jan-Feb;104(1):55-66	Peer-reviewed journal	Italy (Friuli-Venezia-Giulia region)	1995-2009	Malignant mesothelioma (MM)	via Regional Register	statistical analysis of environmental exposure and relationship between pleural plaques and asbestos		834 cases of MM			C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
44	Skammeritz E et al. Dan Med J. 2013 Mar;60(3):A4592	Peer-reviewed journal	Denmark	1943-2009	Malignant mesothelioma (MM)	Data from Danish Cancer Registry			3,394 cases of MM of the pleura, peritoneum and pericardium. 2008-2009: 1.76/100,000 in men; 0.5/100,000 in women	median survival 12.5 months for men, 13.3 months for women		B
45	Pairon JC et al. J Natl Cancer Inst. 2013 Feb 20;105(4):293-301.	Peer-reviewed journal	France	2003-2005	Association between pleural plaques and pleural mesothelioma	Retired or unemployed workers previously occupationally exposed to asbestos were invited to participate in a screening program for asbestos-related diseases in 4	Multicenter study		17 cases MPM			C
46	Delourme J et al. Rev Pneumol Clin. 2013 Feb;69(1):26-35	Peer-reviewed journal	Europe				Review					C
47	Pinto C et al. Cancer Treat Rev. 2013 Jun;39(4):328-39	Peer-reviewed journal	Italy	2008	Malignant pleural mesothelioma	Data from Italian Registry of Malignant Mesothelioma (Second Italian Consensus Conference)	Italian consensus conference report		3.6 (men) and 1.3 (woman) per 100,000	Median survival: 9.8 months		B
48	Helland Å et al. J Thorac Oncol. 2012 Dec;7(12):1858-61	Peer-reviewed journal	Norway	2005- 2009	Malignant Pleural mesothelioma	data from the Cancer Registry of Norway	Population-based study	5 million	377 cases Women: 0.3/100,000; Men 1.5/100,000	median survival 9.3 months in men		B
49	Ameille J. Rev Mal Respir. 2012 Oct;29(8):1035-46	Peer-reviewed journal	France	2003		National Programme for the Surveillance of Mesothelioma	Text of reference		800			C
50	Mirabelli D et al. Cancer Causes Control. 2012 Dec;23(12):2023-9	Peer-reviewed journal	Italy	1962-2004	Bladder cancer		Cohort study					C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
51	Skammeritz E et al. Int J Occup Environ Med. 2011 Oct;2(4):224-36	Peer-reviewed journal	Northern Denmark	1984-2010	Malignant Mesothelioma related to asbestos exposure	medical records from the occupational clinic, medical records from the treating hospitals and the local and national pathological databases	identification of all patients diagnosed with MM from the database of the occupational clinic	study group: 122 patients	MPM 101 cases; peritoneal 11 cases; tunica vaginalis testis 2 cases; 8 multiple serosal surfaces.	median survival rate 1.05 years		C
52	Sorahan T. Occup Med (Lond). 2012 Oct;62(7):496-505	Peer-reviewed journal	UK (England and Wales)	1973-2008	cancer morbidity related to magnetic field exposure	81 842 employees of the former Central Electricity Generating Board of England and Wales	Cohort study					C
53	Brown T et al. Br J Cancer. 2012 Jun 19;107 Suppl 1:S56-70	Peer-reviewed journal	Great Britain	1984-2010	occupational cancer: larynx, lung and mesothelioma	MM cases from the database of the occupational clinic				2046 deaths (2005)		C
54	Berrino F et al. Epidemiol Prev. 2012 Mar-Apr;36(2):136-7	Peer-reviewed journal	Italy		"Asbestos-free" campaign							C
55	Bonnetterre V et al. Am J Ind Med. 2012 Sep;55(9):756-67	Peer-reviewed journal	France (Isère)	1979-2002	cancer in a chlorochemical plant	Plant occupational health service and regional cancer registry	Cohort study					C
56	Comar M et al. Tumori. 2012 Mar-Apr;98(2):210-4	Peer-reviewed journal	Italy		asbestos and SV40 in MPM		molecular epidemiology study					C
57	Marinaccio A et al. BMC Public Health. 2012 Jul 5;12:314	Peer reviewed report	Italy (Valle d'Aosta, Piedmont, Veneto, Lombardy, Friuli-Venezia Giulia, Tuscany, Liguria, Emilia-Romagna, Marche, Apulia, Basilicata, Campania, and	2000 - 2004	Mesothelioma	MM cases diagnosed selected from ReNaM archives and linkage to Italian workers' compensation authority		77.7% of the whole Italian population	9,544 cases (1993 to 2004)			C
58	Carugno M et al. Med Lav. 2012 Jan-Feb;103(1):70-1	Peer-reviewed journal	Italy				Letter to editor					C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
59	López-Abente G et al. Sci Total Environ. 2012 May 1;424:57-62	Peer-reviewed journal	Spain	1997-2006	Pleural cancer	municipal registries	Ecological study			2,146 deaths		C
60	Siesling S et al. Eur J Cancer. 2012 May;48(7):949-60	Peer-reviewed journal	Iceland, Sweden and Norway, Austria, Belgium, France, Germany, Switzerland and The Netherlands, Poland and Slovakia, Malta, Italy, Portugal, Slovenia and Spain and UK and Ireland and Wales	1995-2002	Mesothelioma	population-based data from different European cancer registries (cases selected based on the list of the RACECARE)	Population surveillance study	162.000.000	15263 cases 19/1,000,000 per year Higher incidence in UK, Ireland and lowest in Easter Europe	1-year Survival rate: 37% 5-year survival rate: 5%	11,841 cases 0,238/10,000	C
61	Riaz SP et al. Eur Respir J. 2012 Oct;40(4):965-8. Epub 2012 Jan 26	Peer-reviewed journal	UK (London, Surrey, Sussex and Kent)	1960 - 2009	mesothelioma	data from Thames Cancer Registry (TCR) database	Cohort	European standard population	8,250 patients (2400 new cases in 2008)			C
62	Gramond C et al. Am J Ind Med. 2012 May;55(5):440-9	Review article	France		mesothelioma due to asbestos exposure	National Mesothelioma Surveillance Program (PNSM): 50 mesothelioma + 50 controls	Case-control study (validation study)					C
63	Gogali A et al. Eur Respir J. 2012 Jan;39(1):217-9	Peer-reviewed journal	Greece (Metsovo)	1980-2009	Malignant Mesothelioma	central registries of the two tertiary care hospitals of Ioannina		4,417 inhabitants (2001) 127,753 persons-year (1981-1991-2001)	26 cases (1980-2009): 14 (1980-1994), 12 (1995-2009). cumulative IR 2.04/10,000 person-yrs: 2.2/10,000 (1980-1994), 1.8/10,000			B
64	Orphanos G et al. Hematol Oncol Stem Cell Ther. 2011;4(4):193-4	Peer-reviewed journal	Cyprus	1997-2007	Mesthelioma		Letter to editor					C
65	Marinaccio A, et al. Epidemiol Prev. 2011 Sep-Dec;35(5-6 Suppl 4):185-8	Scientific journal	Italy		mesothelioma and sinonasal cancers	Italian National Mesothelioma Register (ReNaM) and the Sinonasal Cancer Register (ReNaTuNS) records	environmental and surveillance studies					C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
66	Merler E et al. Epidemiol Prev. 2011 Sep-Dec;35(5-6):331-8	Scientific journal	Italy (Veneto region)	1999-2007	mesothelioma due to occupational exposure	record-linkage method with insurance institutions	Comparative study		499 cases (349 due to occupational exposure)			C
67	Dalphin JC. Rev Mal Respir. 2011 Dec;28(10):1230-40	Peer-reviewed journal			asbestos-related diseases		Follow-up studies (review)					C
68	Dunican E et al. Ir Med J. 2011 Oct;104(9):265-8	Peer-reviewed journal			Lung cancer and thoracic malignancies	patients referred to a dedicated Rapid Access Lung Cancer Clinic						C
69	Lacourt A et al. Tumori. 2011 Mar-Apr;97(2):156-9 et al.	Peer-reviewed article	France	1987-1993 1998-2006	Pleural Mesothelioma	Cases selected from a French case-control study (1987-1993) and the French National Mesothelioma Surveillance Program	large population-based case-control study. Occupational asbestos exposure was evaluated		1,041 cases and 1,425 controls			C
70	Costantino C et al. Ig Sanita Pubbl. 2011 Jul-Aug;67(4):455-66	Scientific journal	Italy (Palermo)	2005-2009	asbestos-related diseases	reports from the Prevention and Safety in the Workplace Unit	environmental study					C
71	Kovac V et al. Anticancer Drugs. 2012 Feb;23(2):230-8	Peer reviewed article			Malignant pleural mesothelioma		Phase II trial (gemcitabine + cisplatin)			median progression-free survival was 8.0 months median overall survival was 17.0 months		C
72	Mensi C et al. Med Lav. 2011 Sep-Oct;102(5):409-16	Scientific journal	Italy (Lombardyregion)	2000-2007 (peritoneal) 2000-2001 (pleural)	Peritoneal and pleural mesothelioma	cases from regional mesothelioma registry	Comparative study	> 9 million	N=110 N=515			C
73	Menegozzo S et al. Ann Ist Super Sanita. 2011;47(3):296-304	Peer-reviewed journal	Italy (Naples)	1950 - 2005			Cohort	1247 men (39 933 person-years)		24		C
74	Burdorf A et al. Ann Occup Hyg. 2011 Jul;55(6):565-8.	Peer-reviewed journal	The Netherlands		Lung cancer and mesothelioma		Meta-analysis of 19 cohort studies					C

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75	Mensi C et al. G Ital Med Lav Ergon. 2011 Jul-Sep;33(3 Suppl):96-8	Medical journal	Italy (Lombardy region)	2000 - 2008	Malignant mesothelioma		evaluation of the trend of incidence and asbestos exposure		2,816 cases, 2,671 due to exposure. IR 3.4/100,000 in men; 1.4/100,000 in women			B
76	Moore S et al. Nurs Stand. 2011 May 25-31;25(38):35-8	Scientific journal	UK		mesothelioma	national Mesothelioma Nurse Action Team	nursing care review		2,400 (2011)	median survival 18 months (2007, 2010)		C
77	Brims FJ et al. Clin Respir J. 2012 Jul;6(3):144-9	Peer-reviewed journal	UK (Portsmouth)				retrospective study of thoracoscopy complications					C
78	Marinaccio A et al. Int J Cancer. 2012 May 1;130(9):2146-54.	Peer-reviewed article	Italy	1993-2004	Malignant Mesothelioma	Information from ReNaM database and information about asbestos exposure	case-list of pleural MM recorded by the Italian National Register (ReNaM) and investigation of the modalities of exposure to		9,544 cases 3.49 (per 100,000 inhabitants) for men and 1.25 for women			C
79	Bianchi C et al. Tumori. 2011 Mar-Apr;97(2):156-9	Peer-reviewed journal	Italy (northeastern)	1968-2008	Pleural malignant mesothelioma	cases diagnosed in nonagenarian patients from the Rieste and Monfalcone Hospitals	Review		811 cases: 7 in > 90 years-old			C
80	Mayor S. BMJ. 2011 May 23;342:d3211	Peer-reviewed journal	UK	2009	Lung cancer and mesothelioma		Medical audit in patients that underwent surgery					C
81	Lara B et al. Arch Bronconeumol. 2011 Aug;47(8):389-96	Peer-reviewed journal	Spain (Asturias, Catalonia and Navarra)	2003-2007	Mesothelioma	summary of the respiratory disease registries in Spain	report on general characteristics, objectives and organizational aspects		83 cases			C
82	Bai E et al. Epidemiol Prev. 2011 Jan-Feb;35(1):55-6	Scientific journal			Work environment: prevention and security	ASL di Como	review article on the Occupational Cancer Monitoring					C
83	Massardier-Pilonchery A et al. Rev Mal Respir. 2011 Apr;28(4):556-64	Peer-reviewed journal	Germany, Spain, Finland, Italy, Norway, Poland, and Switzerland		follow-up for post-occupational monitoring		review					C

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84	Chellini E et al. Epidemiol Prev. 2011 Jan-Feb;35(1):47-9	Scientific journal	Italy (Sicilia and Toscana)	1988-2005	mesothelioma registries vs. population-based registries	Italian National Mesothelioma Registry (RENAM) and for the Italian Association of Cancer Registries (AIRTUM)	comparison study					C
85	Merler E. Epidemiol Prev. 2011 Jan-Feb;35(1):8	Scientific journal			Fund for asbestos victims		Comparative study					C
86	Clin B et al. Occup Environ Med. 2011 Nov;68(11):832-6	Peer-reviewed journal	France (Calvados, Normady)	1978-2004	pleuro-peritoneal mesothelioma, lung cancer and colorectal cancer	professional history and occupational exposure of each subject in files held by the company occupational health department	Cohort study: dose-response relationship between occupational asbestos exposure and risk of cancer	2024 subjects occupationally exposed to asbestos	285 cases			C
87	Bianchi C et al. Am J Ind Med. 2011 Jun;54(6):494	Peer-reviewed journal	France		Pleural Mesothelioma in various occupations		Letter to editor					C
88	Hmeljak J et al. Tumori. 2010 Sep-Oct;96(5):667-73	Scientific journal	Slovenia		SV40 as risk factor for malignant pleural mesothelioma	Paraffin-embedded malignant pleural mesothelioma specimens from 103 Slovenian patients						C
89	Mensi C et al. Int J Hyg Environ Health. 2011 Jun;214(3):276-9	Peer-reviewed journal	Italy (Lombardy region)	2000-2009	Pericardial mesothelioma	Lombardy Mesothelioma Registry	Case reports		8 cases 0.09/1,000,000/year			B
90	Riva MA et al. Med Lav. 2010 Nov-Dec;101(6):409-15	Scientific journal	Italy	1960's	Malignant mesothelioma	analysis of scientific and historical literature on the relationship between asbestos exposure and tumours, specially by Italian authors	Biography/historical article					C
91	Krzakowski M. Pneumonol Alergol Pol. 2010;78(6):384-5	Peer-reviewed journal	Poland		Non-small lung cancer and malignant pleural mesothelioma		review on recommendations for systemic treatment					C

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92	McDonald. Ann Occup Hyg. 2010 Nov;54(8):851-7	Peer-reviewed journal	Great Britain USA, Canada	1965-1975 1960-1975	Malignant mesothelioma Malignant mesothelioma		review article			668 cases		C
93	Mirabelli D et al. Occup Environ Med. 2010 Nov;67(11):792-4	Peer-reviewed journal (short report)	Italy	1993-2001	Malignant mesothelioma	cases registered by the national mesothelioma registry (ReNaM)	Summarised data from the ReNaM database on cases with exposures and questionnaires		5173 cases			C
94	Rolland P et al. Am J Ind Med. 2010 Dec;53(12):1207-19	Peer-reviewed journal	France	1998 to 2002	mesothelioma		multicenter population-based case-control study	15 million inhabitants (25% of population)	462 cases and 897 controls			C
95	Kricka O et al. Arh Hig Rada Toksikol. 2009 Nov;60 Suppl:41-3	Peer-reviewed journal	Rijeka (Croatia)	1989 - 2008	Malignant pleural mesothelioma	Retrospective analyses of the records of MPM patients treated at the Pulmonology Department of the Clinic for Internal Diseases, Clinical Hospital Centre Rijeka	Retrospective analyses		121 patients			C

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96	Cvitanović S et al. Arh Hig Rada Toksikol. 2009 Nov;60 Suppl:31-9	Peer-reviewed journal	Split-Dalmatia	2001-2005	malignant pleural mesothelioma	Pneumology Clinic whose workplace or residence could involve exposure to asbestos	with an asbestos-related disease without an asbestos-related disease	1150 patients with respiratory symptoms 1030 patients	52 cases 12 cases			C
97	Decković-Vukres V et al. Arh Hig Rada Toksikol. 2009 Nov;60 Suppl:23-30	Peer-reviewed journal	Croatia	2002-2007	mesothelioma, asbestosis, and pleural plaque		study to identify the incidence and prevalence of asbestos-related diseases, based on the Hospital Morbidity Database and General Mortality Database of the Croatian National Institute of Public Health		6 cases (mesothelioma)	1.2 per 100.000 people		C
98	Arh Hig Rada Toksikol. 2009 Nov;60 Suppl:15-21	Peer-reviewed journal	Croatia	1991-2006	Malignant pleural mesothelioma	data from workers from an asbestos-cement factory	review of asbestos exposure and asbestos-related diseases in view of the asbestos ban		40			C
99	Cvitanović S et al. Arh Hig Rada Toksikol. 2009 Nov;60 Suppl:1-2	Scientific journal	Croatia		asbestos-related diseases		introductory journal article					C
100	Fazzo et al. Epidemiol Prev. 2010 May-Jun;34(3):87-92.	Peer-reviewed journal	Sicilian region, Italy	1958 - 1993	pleural mesothelioma	cohort was enumerated by the local committee of formerly exposed workers with record-linkage to Sicilian centre of the National mesothelioma	cohort		Standardised incidence ratio (SIR) for mesothelioma in the overall cohort was 251 (4 observed, 0.02 expected).			C

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101	Gilg Soit Ilg et al. Eur J Epidemiol. 2010 Nov;25(11):799-806.	Peer-reviewed journal	France		relationship between mesothelioma and occupational asbestos	cases registered by the French National Mesothelioma Surveillance Program	two case-control studies					C
102	Marinaccio et al. Occup Environ Med. 2010 Nov;67(11):760-5	Peer-reviewed journal	Italy	1993 - 2004	extrapleural malignant mesothelioma	Italian National Mesothelioma Register (ReNaM)		pleural/non-pleural ratio is 12.5/1 (13.8/1 for the peritoneal site)	681 cases Standardised incidence rates (per million inhabitants, 2004) were 2.1 and 1.2 cases for the peritoneal site (in men and women, respectively), 0.2 cases for the tunica vaginalis testis, and 0.1 in the pericardial site	Pericardial and peritoneal MM: median survival 5 - 6.9 months. pleural MM: median survival 7.9-10 months.		C
103	Martines et al. G Ital Med Lav Ergon. 2010 Apr-Jun;32(2):154-61.	Peer-reviewed journal	Italy				study and develop an algorithm based on the findings of occupational anamnestic information provided by a large group of workers					C
104	Goldberg et al. Occup Environ Med. 2010 Jun;67(6):417-21	Peer-reviewed journal	France	1998-2008	mesothelioma			26 districts 1,916,494 France: 2,583,493	SIR (0.80/100,000)	SMR (0.76/100,000)		C
105	Marinaccio. Med Lav. 2010 Mar-Apr;101(2):146-8	Scientific journal	Lombardy region, north of Italy	2000-2010	mesothelioma	Lombardy Mesothelioma Registry		9,1 million				C
106	Mensi et al. J Formos Med Assoc. 2010 May;109(5):389	Scientific journal	Lombardy region, north of Italy	2000-2010	mesothelioma	Lombardy Mesothelioma Registry	Letter to editor		1848			C
107	Thorgeirsson et al. Chest. 2010 Apr;137(4):1005-6	Scientific journal	Iceland	1984-2007	diffuse malignant mesothelioma and localized solitary fibrous tumors of the pleura		Letter to editor		35 4.0/million			C

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108	Vudrag et al. Arh Hig Rada Toksikol. 2010 Mar;61(1):45-52	Peer-reviewed journal	Slovenia	1992-1996	Mesothelioma			49,859 (districts) 1,949,750	21.4/100,000			C
109	Ugolini et al. Lung Cancer. 2010 Nov;70(2):129-35	Peer-reviewed journal			Malignant mesothelioma	PubMed database	Comparative study on publication trends					C
110	Mise et al. Coll Antropol. 2009 Dec;33(4):1245-50	Peer-reviewed journal	Croatia (Split-Dalmatian county)	2000-2007	MPM	retrospective collection of medical records of Department of Pulmonary Diseases Univeersity	retrospective study		3.55/100,000			B
111	Lalić et al. Coll Antropol. 2009 Dec;33(4):1223-8	Peer-reviewed journal	Croatia (Primorsko-Goranska county)					400.000				C
112	Salermo et al. Ann Ig. 2009 Sep-Oct;21(5):501-5	Scientific journal	Italy (Trino city, Vercelli province)		neoplasias of the mouth, nervous system, peritoneum in addition to eukaemias and							C
113	Strand et al. Am J Ind Med. 2010 Jan;53(1):64-71	Peer-reviewed journal	Norway	1950-2004	malignant mesothelioma, lung cancer, and laryngeal, pharyngeal, stomach, and colorectal	data collection on all branches of the Royal Navy, inclusive of the Coast Guard, the Coastal Artillery, and the Fleet	historical cohort to evaluate the risk of asbestos-related cancers					C
114	Driece at al. J Expo Sci Environ Epidemiol. 2010 Jul;20(5):478-85	Peer-reviewed journal					Exposure to environmental asbestos					C
115	Neumann et al. Med Klin (Munich). 2009 Oct 15;104(10):765-71	Medical journal	Germany		Malignant peritoneal mesothelioma, including mesothelioma of tunica		medical insurance aspects					C
116	Bianchi et al. Med Lav. 2009 Jul-Aug;100(4):313	Scientific journal			Malignant mesothelioma	Finance Pollice personnel						C

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117	Zona, Bruno Ann Ist Super Sanita. 2009;45(2):147-61.	Peer-reviewed journal	Italy				review of international and italian regional practices to a proposed operational model					C
118	Nemo et al. Epidemiol Prev. 2009 Jan-Apr;33(1-2):59-64	Peer-reviewed journal	Italy	1957-1995	asbestos	Livorno harbour	description of quantities, type of packaging and origin of asbestos fibers					C
119	Graziano et al. Epidemiol Prev. 2009 Jan-Apr;33(1-2):37-44	Peer-reviewed journal	Italy (Taranto province)		Lung, pleura, pleuric mesothelioma, bladder malignancies, brain, non-Hodgkin lymphoma,	Jonico Salentino Cancer registry		581,508 inhabitants				C
120	Le Stang et al. Int J Cancer. 2010 Jan 1;126(1):232-8	Peer-reviewed journal	France	1980-2005	malignant pleural incidence	French network of cancer registries (FRANCIM) and the French National Mesothelioma Surveillance Program (PNSM) registries			0.6/100,000 (1980) 1.4/100,000 (2000)	1.0/100,000 (1980) 1.7/100,000 (2000)		C
121	Marinaccio. Epidemiol Prev. 2009 Jul-Oct;33(4-5 Suppl 2):80-4.	Scientific journal	Italy		Cancer registers in face of the new law (2008)	ReNaM & ReNaTuns						C
122	Tarrés et al. Arch Bronconeumol. 2009 Sep;45(9):429-34	Scientific journal	Spain (12 cities of Vallès Occidental, Barcelona)	2000-2006	asbestos-related diseases	medical data from 12 health centers and 1 hospital	retrospective study	417.715	MPM: 1.5/100,000/ano			C
123	Merler et al. Med Lav. 2009 Mar-Apr;100(2):120-32	Medical journal	Italy (Veneto region)	1987-2006	mesothelioma due to asbestos exposure	search for mesotheliomas followed by interviews and collection of job data held over their lifetime		4.5 million inhabitants				C
124	Barbieri et al. G Ital Med Lav Ergon. 2008 Oct-Dec;30(4):329-3	Scientific journal	Italy (province of Brescia)	1977-2006	Malignant mesothelioma	Mesothelioma Registry of Brescia			8 cases			C

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125	Brauer et al. Ugeskr Laeger. 2009 Feb 7;171(6):433-6	Scientific journal	Denmark		asbestos-related cancers		Overview of screening programs for early detection					C
126	Cukić et al. Bosn J Basic Med Sci. 2008 Nov;8(4):361-6.	Scientific journal		1998-2007	Malignant pleural mesothelioma (MPM)	cases treated in Clinic for Pulmonary Diseases and Tuberculosis "Pedičevići"	retrospective study					C
127	Ugolini et al. Cancer Epidemiol Biomarkers Prev. 2008 Nov;17(11):3013-9. Erratum in: Cancer Epidemiol Biomarkers Prev. 2009 Apr;18(4):1331	Peer-reviewed journal	Italy (Liguria)	2008	Pleural malignant mesothelioma and lung cancer	CREST biorepository (n=1,590 subjects recruited)	Biological samples of (a) patients with pleural malignant mesothelioma and lung cancer, (b) patients with nonneoplastic respiratory conditions, and (c) control subjects.		209			C
128	Sichletidis et al. Respiration. 2009;78(1):63-8.	Peer-reviewed journal	Greece		asbestos-related diseases		prospective study: mortality rate on exposed workers			52 deaths - 28 cancers: 16 lung cancers, 0 mesothelioma; 23 cardiovascular; 1 cirrhosis		C
129	Musti et al. Int Arch Occup Environ Health. 2009 Mar;82(4):489-97	Peer-reviewed journal	Italy (city of Bari)	1993-2003		Regional mesothelioma register (RMR)	spatial case-control study					C
130	Müller et al. Chirurg. 2008 Mar;Suppl:99-102	Peer-reviewed journal										C no abstract available. Article in German.
131	Barbieri et al. Med Lav. 2008 May-Jun;99(3):187-93	Peer-reviewed journal	Italy (Brescia)			case collection from Mesothelioma Registry of Brescia	questionnaire to sewing-machine maintenance personnel		10			C
132	Mirabelli et al. Epidemiol Prev. 2007 Mar-Jun;31(2-3):132-8	Peer-reviewed journal	Italy (Piedmont region)	1990-2001	Malignant mesothelioma	National Mesothelioma Registry			1990-1992: 1.1/100,000 1999-2001: 2.6/100,000			C

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133	Stura et al. Epidemiol Prev. 2007 Mar-Jun;31(2-3):127-31	Peer-reviewed journal	Italy (Piedmont region)	1990-2001	MPM				2.7/100,000 in men, 1.2/100,000 in women			C
134	Teslariu et al. Rev Med Chir Soc Med Nat Iasi. 2008 Jul-Sep;112(3):769-74	Peer-reviewed journal										C Article in Romanian.
135	Mirabelli et al. Occup Environ Med. 2008 Dec;65(12):815-9	Peer-reviewed journal	Italy (Balangero)		Pleural mesothelioma	cases on Registry if Mesotheliomas of Piedmont						C
136	Gamble. Regul Toxicol Pharmacol. 2008 Oct;52(1 Suppl):S121-3.	Peer-reviewed journal	Souh Africa; Montana, USA; Turkey, Greece, Corsica New Caledonia and Cyprus; Minnesota, USA				Rapporteur's Report					C
137	Kashanskiĭ. Med Tr Prom Ekol. 2008;(3):15-21	Peer-reviewed journal	Russia	1881-2006	Mesothelioma		Systematic review					C
138	McNamee et al. Occup Environ Med. 2008 Dec;65(12):808-14	Peer-reviewed journal	UK	1996-2005	work-related skin and respiratory diseases: non-malignant pleural disease, asthma, mesothelioma and pneumoconiosis							C
139	Menegozzo et al. G Ital Med Lav Ergon. 2007 Jul-Sep;29(3 Suppl):644	Peer-reviewed journal	Italy (Pelezzano)	2000-2007	malignant mesothelioma				Salerno: 41 cases Pellezzano: 5 cases			C
140	Menegozzo et al. G Ital Med Lav Ergon. 2007 Jul-Sep;29(3 Suppl):642-4	Peer-reviewed journal	Italy (Campania)	1996-2007	Malignant mesothelioma	Campania Mesothelioma Register data			492 cases			C
141	Venuti et al. G Ital Med Lav Ergon. 2007 Jul-Sep;29(3 Suppl):639-40	Peer-reviewed journal	Italy (Sicily)	1998-2005	Malignant pleural mesothelioma (MPM)	Data consultation: Mesothelioma Sicilian Register, Mesothelioma Italian Register and Health Superior Institute						C

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142	Montomoli et al. G Ital Med Lav Ergon. 2007 Jul-Sep;29(3 Suppl):332-3	Peer-reviewed journal	Siena		Work related mesothelioma							C
143	Epidemiol Prev. 2007 Jul-Aug;31(4 Suppl 1):1-84.	Scientific journal	Italy (Lower Iseo Lake)	1977-2005	Malignant mesothelioma		National conference report		6.8/100,00			C
144	Roberti et al. Epidemiol Prev. 2007 Nov-Dec;31(6):309-16	Peer-reviewed journal	Italy (Veneto region)	1988-2002	Malignant mesothelioma			4.500.000	2.94/100,000			C
145	Mensi et al. Epidemiol Prev. 2007 Sep-Oct;31(5):283-9	Peer-reviewed journal	Italy (Lombardo region)	2000-2004	Malignant mesothelioma (MM)	Lombardy Mesothelioma Register (LMR)			2.4/100,000 per year			C
146	De Zotti. Med Lav. 2008 Jan-Feb;99(1):58-9.	Peer-reviewed journal	Italy (Fuiili-Venice Guilia)		Mesothelioma							C
147	Lundstig et al. Anticancer Res. 2007 Nov-Dec;27(6B):4159-61	Peer-reviewed journal			SV40 DNA in mesothelioma tissue							C
148	Chapman et al. Thorax. 2008 May;63(5):435-9.	Peer-reviewed journal	UK (Leeds)	2002-2005	Malignant mesothelioma	patients' hospital records	retrospective and prospective study	750.000	146 cases	median survival 8.9 months		C
149	Constantopoulos. Regul Toxicol Pharmacol. 2008 Oct;52(1 Suppl):S110-5	Peer-reviewed journal	Greece, Turkey, Cyprus, Corsica and New Caledonia		mesothelioma due to asbestos exposure							C
150	Marinaccio et al. Int Arch Occup Environ Health. 2008 Aug;81(8):993-1001	Peer-reviewed journal	Italy	1988-2001	Malignant mesothelioma				148 cases			C
151	Sinninghe Damsté et al. Ned Tijdschr Geneeskd. 2007 Nov 2;151(44):2452-9	Peer-reviewed journal	The Netherlands (Twente region)	1989-2002	Pleural mesothelioma in women	cases on region of Twente registers by the national cancer register.	Ecological study		28 cases			C
152	van der Laan. Ned Tijdschr Geneeskd. 2007 Nov 3;151(44):2422-5	Peer-reviewed journal	The Netherlands (Goor)		Mesothelioma							C

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153	Bottazzi. Epidemiol Prev. 2007 Jul-Aug;31(4 Suppl 1):31-4.	Peer-reviewed journal	Germany France Italy Belgium Spain	2003			Convention report		788 cases 421 cases 389 cases 92 cases 6 cases			C
154	Mensi et al. Epidemiol Prev. 2007 Jul-Aug;31(4 Suppl 1):27-30	Peer-reviewed journal	Italy (Lombardy)	2000-2005		Lombardy Mesothelioma Register (LMR)			2.4/100,000 (2000)			C
155	Marinaccio et al. Epidemiol Prev. 2007 Jul-Aug;31(4 Suppl 1):23-6	Peer-reviewed journal	Italy	2001		Regional Operating Center	epidemiological surveillance by Italian mesothelioma register (ReNaM)		2.98/100,000 in men 0.98/100,000 in women			C
156	Barbieri et al. Epidemiol Prev. 2007 Jul-Aug;31(4 Suppl 1):16-22	Peer-reviewed journal	Italy (Lower Iseo Lake area)	1977-2006		hospital observation	epidemiological surveillance	43,000 inhabitants	45 cases female MPM 6.8/100,000			C
157	Burkitt. J Natl Cancer Inst. 2007 Dec 5;99(23):1750-2	Peer-reviewed journal	Australia						32/1,000,000	1-year survival rate 42%; 5-year survival rate 5%		C
158	Marinaccio et al. Eur J Cancer. 2007 Dec;43(18):2722-8.	Peer-reviewed journal	Italy	1993-2001	Malignant mesothelioma (MM)	cases collected by the Italian mesothelioma register (ReNaM)	multicenter study		2,544 cases with asbestos exposure history			C
159	Hemminki, Hussain. Int J Cancer. 2008 Mar 1;122(5):1200-1	Peer-reviewed journal	Sweden	1990-2005	Pleural mesothelioma	Data collected from Swedish Cancer Registry			men: 1.5/100,000 women: 0.3/100,000			C
160	Kelsh et al. Occup Med (Lond). 2007 Dec;57(8):581-9	Peer-reviewed journal	Australia		mesothelioma	Australian Mesothelioma Registry						C
161	Peřclová et al. Cent Eur J Public Health. 2007 Sep;15(3):99-102	Peer-reviewed journal	Czech Republic		mesothelioma				0.5/100,000			C
162	Bianchi et al. Med Lav. 2007 Sep-Oct;98(5):374-80.	Peer-reviewed journal	Italy (Triesle province)	2001-2006	pleural mesothelioma	diagnosed at the Department of Surgery, Thoracic Surgery Unit, Trieste University	retrospective study	240.000				C
163	Ugolini et al. Mutat Res. 2008 Mar-Apr;658(3):162-71	Peer-reviewed journal			Malignant mesothelioma (MM)	PubMed	literature review					C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
164	Mak et al. Thorax 2008;63:160-166.	Peer-reviewed journal	South East England, UK	1985-2002	Mesothelioma	Data collected from the Thames Cancer Registry database			4% annual percentage increase in the age standardised incidence rate for South East England men between 1985 and 2002	5753 patients		C
165	Burdorf et al. Occup Environ Med. 2007 Dec;64(12):839-42.	Peer-reviewed journal	Sweden & the Netherlands	1989-2003	peritoneal mesothelioma	Swedish and Netherlands Cancer Registers			Sw: 1.8/100,000 NL: 0.6/100,000			C
166	Hansen et al. Ugeskr Laeger. 2007 Apr 30;169(18):1674-8.	Peer-reviewed journal	Denmark	1994-2002	pleural mesothelioma and adenocarcinoma of the sinosal cavities	collected from the Danish Cancer Registry			MPM: 695 cases			C
167	Le Neindre et al. Rev Epidemiol Sante Publique. 2007 Apr;55(2):123-31.	Peer-reviewed journal	France (Normandy)	1995-2002	Malignant mesothelioma	regional mesothelioma registry			141 cases			C
168	Tweedale. Int J Occup Environ Health. 2007 Jan-Mar;13(1):70-9.	Peer-reviewed journal	UK		asbestos-related cancers							C
169	Bianchi, Bicanchi. J Occup Environ Med. 2007 Apr;49(4):359	Peer-reviewed journal			malignant mesothelioma	MM in telephone workers	Comment letter					C
170	Ascoli et al. Am J Ind Med. 2007 May;50(5):357-69.	Peer-reviewed journal	Italy		Malignant mesothelioma	Mesothelioma Registries and Medline	literature review					C
171	Proiett et al. Monaldi Arch Chest Dis. 2006 Dec;65(4):210-6	Disease archive	Italy (Catania, Sicily)	2005			retrospective study					C
172	Mariottini. Epidemiol Prev. 2006 Nov-Dec;30(6):307	Scientific journal			environmental epidemiology		Letter to editor					C
173	Geoffroy-Perez et al. Rev Epidemiol Sante Publique. 2006 Dec;54(6):475-83.	Peer-reviewed journal	France	1998-1999	reporting pleural mesothelioma cases	hospital national database vs. National Mesothelioma Surveillance Program						C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
174	Isele H. MMW Fortschr Med. 2006 Oct 12;148(41):8	Scientific journal					Comment letter					C
175	Tomatis et al. Epidemiol Prev. 2006 Jul-Oct;30(4-5):289-94	Peer-reviewed journal			pathogenetic role os asbestos in mesothelioma		review					C
176	Carnigliaro et al. Epidemiol Prev. 2006 Jul-Oct;30(4-5):227-31	Peer-reviewed journal	Italy (Biancavilla, Sicily)	1995-2003								C
177	Pannelli et al. Med Lav. 2006 Sep-Oct;97(5):682-93.	Peer-reviewed journal		10 y	incidence of mesothelioma vs asbestos consumption	cancer registries from Cancer Incidence in Five Continents, Vol. VII and VIII, and, when appropriate, standardized rate ratio (SRR) with confidence interval were estimated.			highest incidence rates Liguria, Maastricht and Scotland, North East regions and Piedmont (Italy)			C
178	Bruno et al. Ann N Y Acad Sci. 2006 Sep;1076:778-83	Peer-reviewed journal	Italy (Biancavilla, Sicily)	1980-1997			environmental study					C
179	Tümmers et al. MMW Fortschr Med. 2006 Sep 28;148(39):5	Peer-reviewed journal			Pleural mesothelioma		case report					C
180	Günther, Wildberger. Eur Radiol. 2007 May;17(5):1193-9.	Peer-reviewed journal	Germany (Aachen)	2005	lung cancer		cohort					C
181	Brown et al. Cancer. 2006 Dec 1;107(11):2741-2; author reply 2742	Peer-reviewed journal	Sweden, Denmark, Finland, and Norway	1943-2002	mesothelioma	population-based cancer registries			1.42/100,000			C
182	Marinaccio et al. Med Lav. 2006 May-Jun;97(3):482-7.	Peer-reviewed journal	Italy	1993-2003	mesothelioma	ReNaM	epidemiological surveillance					C
183	Mensi et al. Med Lav. 2006 Jan-Feb;97(1):82	Scientific journal	Italy				Letter to editor					C
184	Camidge et al. Br J Cancer. 2006 Sep 4;95(5):649-52.	Peer-reviewed journal	UK (Scotland)	1981-1999	mesothelioma detection rate							C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
185	Sichletidis et al. Am J Ind Med. 2006 Aug;49(8):634-41.	Peer-reviewed journal	Greece (Almopia)	2003	pleural plaques		prospective study					C
186	Neri et al. Int J Hyg Environ Health. 2006 Jul;209(4):393-8	Peer-reviewed journal	Finland & Italy		Malignant pleural mesothelioma	genotyping analysis	comparative study					C
187	Laakkonen et al. Occup Environ Med. 2006 Nov;63(11):726-33.	Peer-reviewed journal	Finland	1971-1995	respiratory cancers	Record linkage with the Finnish Cancer Registry	cohort follow-up		SIR 4.57			C
188	Huuskonen, Rantanen. Am J Ind Med. 2006 Mar;49(3):215-20.	Peer-reviewed journal	Finland	1987-2005	asbestos-related diseases	Finnish Institute of Occupational Health (FIOH)						C
189	Goldberg et al. Occup Environ Med. 2006 Jun;63(6):390-5	Peer-reviewed journal	France	1999-2001	mesothelioma detection rate	French National Mesothelioma Surveillance Program		16 million	449			C
190	Ekberg-Aronsson et al. Lung Cancer. 2006 Jan;51(1):21-9	Peer-reviewed journal	Sweden (Malmö)		lung cancer							C
191	Bolognesi et al. Cancer Epidemiol Biomarkers Prev. 2005 Jul;14(7):1741-6	Peer-reviewed journal			Malignant pleural mesothelioma	cytogenetic study	case control study					C
192	Hollen et al. Support Care Cancer. 2006 Jan;14(1):11-21	Peer-reviewed journal			Quality of life in MPM patients		validation study					C
193	Filiberti, Motanaro. Lung Cancer. 2004 Aug;45 Suppl 1:S25-7.	Peer-reviewed journal	Italy	1990-1994	Pleural mesothelioma	ReNaM	review			Median survival 1Y 32% 3Y 10% 5Y 4%		C
194	Neumeister et al. Med Klin (Munich). 2001 Dec 15;96(12):722-9	Peer-reviewed journal		> 2001	Pleural mesothelioma		review					C
195	Bonazzina et al. Epidemiol Prev. 1997 Oct-Dec;21(4):279-82	Peer-reviewed journal	Italy (Lombardy region)	1978-1993	Pleural mesothelioma	information available in the District				17 deaths		C
196	McLean, Patel. Scott Med J. 1997 Apr;42(2):37-9.	Peer-reviewed journal	UK (Glasgow)	1987-1992	Malignant pleural mesothelioma	Local cancer registry	retrospective study		144 cases	median survival 30 weeks		C

#	Reference	Type of Source	Region	Collection years	Case definition	Data collection method	Design	Reference population size	Incidence	Mortality	Prevalence	Class / Comments
197	Coëtmeur D. Rev Mal Respir. 1996 Jul;13(3):318.	Peer-reviewed journal	France (Nantes-Saint Nazaire)	1956-1992	Malignant pleural mesothelioma		comment in a letter to editor					C
198	Chailleux et al. Rev Mal Respir. 1995;12(4):353-7.	Peer-reviewed journal	France (Nantes-Saint Nazaire)	1956-1992	Malignant pleural mesothelioma	Loire-Atlantique registries, private physicians and hospital service, and retrospective inquiry to patients	comparative study		1956-1984: 125 cases; incidence 2.6/1,000,000 1985-1992: 92 cases, incidence 10.9/1,000,000			C
199	Woitowitz. Med Klin (Munich). 1987 Aug 21;82(17):578-81, 503	Peer-reviewed journal			Malignant pleural mesothelioma							C
200	Biava et al. Med Lav. 1983 Jul-Aug;74(4):260-5.	Peer-reviewed journal	Italy (Trieste province)		Pleural mesothelioma and the role of occupational exposure to asbestos							C
201	Mirabella. Pathologica. 1982 Mar-Apr;74(1030):215-20	Peer-reviewed journal			Pericardial mesothelioma		review					C
202	McDonald JC, McDonald AD. Prev Med. 1977 Sep;6(3):426-42	Peer-reviewed journal			Mesothelioma							C
203	Rubino et al. Br J Ind Med. 1972 Oct;29(4):436-42	Peer-reviewed journal	Italy (Piedmont)	1960-1970	Pleural mesothelioma				54 cases			C
204	Bittersohl G, Ose H. Z Gesamte Hyg. 1971 Nov;17(11):861-4	Peer-reviewed journal	Germany									C

Classification: A - Perfectly adequate: Article presented prevalence data on malignant mesothelioma, all sites, (or, alternatively, incidence data and mean duration of the condition of interest) collected between 2010 and 2016, concerning the 28 Member States of the European Union plus Iceland, Liechtenstein and Norway.

B - Adequate: Article presented prevalence or incidence data on malignant mesothelioma, all sites, collected between 2006 and 2016, concerning one or more countries belonging to the European Union Member States (EU28) plus Iceland, Lichenstein and Norway, or, alternatively, in malignant pleural mesothelioma.

C - Inadequate: One of the search criteria was not defined, or was not described in accordance with the definitions established above

28 Member States in the European Union: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Ireland, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Spain, Slovakia, Slovenia, Sweden and the United Kingdom.

Annex 2. Estimation of prevalence based on references previously classified as B

#	Reference	Region	Collection years	Case definition	Reference population size	Incidence	Mortality/Survival	Estimated Prevalence
2	Magnani et al. Med Lav. 2015 Sep 9;106(5):325-32	Italy	2011	Pleural mesothelioma		3.64 per 100,000 person/years in men and 1.32 in women		
6	Marinaccio et al. Occup Environ Med. 2015 Sep;72(9):648-655	Italy	1993-2008	Pleural mesothelioma		3.84 /100,000 for men and 1.45 /100,000 for women (in 2008) Total 15,845 mesothelioma cases (1993-2008)		
7	Beckett et al. 2015 Lung Cancer. 2015 Jun;88(3):344-8	UK (England and Wales)	2008-2012	Malignant pleural mesothelioma (MPM)	53.5 million in England + 3.1 million in Wales (mid 2012)	8740 cases submitted to the audit [England : (2008: 1310; 2009:1688; 2010: 1717 cases; 2011: 1735 cases; 2012: 1885 cases) Wales: (2008: 86; 2009: 67; 2010: 91 cases; 2011:82 cases; 2012: 79 cases)] =3.5/100,000	Overall median survival was 9.5 months (median survival increased from of 9.2 months in 2008 to 10.5 months in 2012), with a 1YS of 41.4% and 3YS of 12.0%.	1Y=0.49/10,000 3Y= 0.62/10,000
15	Langhoff et al. Dan Med J. 2014 Sep;61(9):A4902.	Denmark (Northern Jutland)	1996 to 2012	Malignant Mesothelioma of the pleura		3.4/100,000 in men; 0.54/100,000	Mortality rate 0.0057% Median survival 12 months Women: 1-year survival of 58%; 5-year survival of 0%	0.39/10,000
19	Bruno et al. Ann Ist Super Sanita. 2014;50(2):111-8.	Italy (Biancavilla, Sicily)	1998 - 2011	malignant mesothelioma		28 cases (1998-2011) overall Standardized Incidence Ratio (SIR) was 5.76 (95% CI 3.76-8.44) respectively, 3.69 (95% CI 1.97-6.32) in men and 13.08 (95% CI 6.97-22.00) in women.		
23	Ascoli et al. Cancer Epidemiol. 2014 Jun;38(3):273-8.	Italy (Lazio region)	2001-2012	mesothelioma	5.5 million inhabitants	791 cases		
25	Jennings et al. Cancer Epidemiol. 2014 Feb;38(1):35-41.	Republic of Ireland	1994-2009	Malignant pleural mesothelioma		337 cases (18.2 cases per million (cpm) per year)	Survival: 197 days in males and 253 days in females	0.13/10,000
34	Rosell-Murphy et al. BMC Public Health. 2013; 13: 723	Spain (Barcelona)	2011 - 2013	Mesothelioma	174,515	17/year 51 in the 3 years		
35	Budroni et al. Ann Ital Chir. 2014 May;Jun;85(3):244-8	Italy (Sassari)	1992-2010	Malignant pleural mesothelioma		70 cases males: 1.2/100,000 females: 0.3/100,000	Mortality rates males: 0.6/100,000 females: 0.2/100,000	Males: 0.18/10,000 Females: 0.04/10,000
38	Romeo al. Med Lav. 2013 Mar-Apr;104(2):115-25	Italy (Lazio Region)	2001-2009	Malignant Mesothelioma		600 cases 1.8 in men and 0.5 in women per 100,000 inhabitants		
39	Ried et al. Chirurg. 2013 Nov;84(11):987-93	Germany (Regensburg)	1998-2011	MPM		0.8/100,000 inhabitants	overall median survival 14-18 months (1-year survival rate 62 %, 3-year survival rate 15 %)	1Y= 0.13/10,000 3Y = 0.17/10,000

#	Reference	Region	Collection years	Case definition	Reference population size	Incidence	Mortality/Survival	Estimated Prevalence
44	Skammeritz E et al. Dan Med J. 2013 Mar;60(3):A4592	Denmark	1943-2009	Malignant mesothelioma (MM)		3,394 cases of MM of the pleura, peritoneum and pericardium. 2008-2009: 1.76/100,000 in men; 0.5/100,000 in women	median survival 12.5 months for men, 13.3 months for women	1Y = 0.195/10,000
47	Pinto C et al. Cancer Treat Rev. 2013 Jun;39(4):328-39	Italy	2008	Malignant pleural mesothelioma		3.6 (men) and 1.3 (woman) per 100,000	Median survival: 9.8 months	1Y = 0.29/10,000
48	Helland Å et al. J Thorac Oncol. 2012 Dec;7(12):1858-61	Norway	2005- 2009	Malignant Pleural mesothelioma		377 cases Women: 0.3/100,000; Men 1.5/100,000	median survival 9.3 months in men	1Y = 0.116/10,000
63	Gogali A et al. Eur Respir J. 2012 Jan;39(1):217-9	Greece (Metsovo)	1980-2009	Malignant Mesothelioma	4,417 inhabitants (2001) 127,753 persons-year (1981-1991-2001)	26 cases (1980-2009): 14 (1980-1994), 12 (1995-2009). cumulative IR 2.04/10,000 person- yrs: 2.2/10,000 (1980-1994), 1.8/10,000 (1995-2009)		
75	Mensi C et al. G Ital Med Lav Ergon. 2011 Jul-Sep;33(3 Suppl):96-8	Italy (Lombardy region)	2000 - 2008	Malignant mesothelioma		2,816 cases, 2,671 due to exposure. IR 3.4/100,000 in men; 1.4/100,000 in women		
89	Mensi C et al. Int J Hyg Environ Health. 2011 Jun;214(3):276-9	Italy (Lombardy region)	2000-2009	Pericardial mesothelioma		8 cases 0.09/1,000,000/year		
110	Mise et al. Coll Antropol. 2009 Dec;33(4):1245-50	Croatia (Split-Dalmatian county)	2000-2007	MPM		3.55/100,000		
60	Siesling S et al. Eur J Cancer. 2012 May;48(7):949-60	Austria, Belgium, France, Germany, Iceland, Ireland, Italy, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, The Netherlands, UK and	1995-2002	Mesothelioma	162.000.000	15263 cases 19/1,000,000 per year Higher incidence in UK, Ireland and lowest in Easter Europe	1-year Survival rate: 37% 5-year survival rate: 5%	11,841 cases 0,238/10,000