

*Ministero dell'Istruzione dell'Università e della Ricerca*

Dipartimento per la formazione superiore e per la Ricerca  
Direzione Generale per il Coordinamento, la promozione e la valorizzazione della Ricerca

PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – Bando 2017  
Prot. 20173X8WA4

**PART A**

**1. Action line**

Main line/Linea Principale

**2. Research project title**

FIBRES: a multidisciplinary mineralogical, crystal-chemical and biological project to amend the paradigm of toxicity and cancerogenicity of mineral fibres.

**3. Duration (months)**

36 months

**4. Main ERC field**

PE - Physical Sciences and Engineering

**5. Possible other ERC field**

LS - Life Sciences

**6. ERC subfields**

1. PE10\_10 Mineralogy, petrology, igneous petrology, metamorphic petrology
2. PE10\_9 Biogeochemistry, biogeochemical cycles, environmental chemistry
3. LS7\_10 Environment and health risks, occupational medicine

## 7. Key Words

n°	Testo inglese
1.	mineralogy
2.	crystal chemistry
3.	environmental mineralogy
4.	environmental toxicology
5.	health risks
6.	zeolite

## 8. Principal Investigator

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(Surname)

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(Name)

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## 9. List of the Research Units

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## 10. Brief description of the research proposal

The mechanisms by which mineral fibres, and especially asbestos, prompt adverse effects in vivo remain poorly understood because the role of all their crystal-chemical-physical parameters to the toxicity/carcinogenicity potential has not been properly assessed yet. This project is aimed to fill this gap and recast the existing mechanistic 'fibre toxicity paradigms'. The new approach includes the role of active surface iron, biodegradability and the 'Trojan horse effect' (cellular release of ion toxic cargo from the dissolving fibres), and ion exchange of the zeolite fibres during the phagocytosis process which may interfere with the biochemical signalling prompting the programmed death (apoptosis) of damaged cells. The strong mineralogical and physical-chemical know how of the team ensures a deep crystal-chemical characterization of the fibres while the interdisciplinary approach permits the understanding of the in vivo toxicity mechanisms to put the basis of quantitative models of bio-chemical interaction of the fibres inducing adverse effects. The biological activities of the fibres will be verified on innovative 3D physiological in vitro models and the final models of toxicity/pathogenicity validated by competent authorities (e.g. the IARC).

## 11. Total cost of the research project, per single item

Associated Investigator	item A.1	item A.2.1	item B	item C	item D	item E	sub-total	item F	Total
GUALTIERI Alessandro	14.563	48.000	37.538	20.000	9.899	20.000	150.000	19.500	<b>169.500</b>
RANERI Simona	2.246	50.000	31.348	500	406	500	85.000		<b>85.000</b>
BALLIRANO Paolo	10.135	0	6.081	50.000	8.784	25.000	100.000		<b>100.000</b>
OTTAVIANI Maria Francesca	11.237	24.000	21.142	10.000	8.621	25.000	100.000		<b>100.000</b>
BASSI Anna Maria	11.628	24.000	21.377	1.000	1.995	55.000	115.000		<b>115.000</b>
PROCOPIO Antonio Domenico	5.478	48.000	32.087	1.000	3.435	10.000	100.000		<b>100.000</b>
<b>Total</b>	<b>55.287</b>	<b>194.000</b>	<b>149.573</b>	<b>82.500</b>	<b>33.140</b>	<b>135.500</b>	<b>650.000</b>	<b>19.500</b>	<b>669.500</b>

- item A.1: Enhancement of months/person of permanent employees
- item A.2.1: Cost of contracts of non-employees, specifically to recruit
- item B: Overheads (flat rate equal to 60% of the total cost of staff, A.1 + A.2.1, for each research unit)
- item C: Cost of equipment, instruments and software
- item D: Cost of consulting services and similar
- item E: Other operating costs
- item F: Prize (automatically calculated as 3% of total cost of the project)

## PART B

### B.1

#### 1. Abstract

MINERAL FIBRES are ubiquitous on the Earth and compose a significant fraction of the airborne particulate. The vast realm of mineral fibres includes asbestos minerals and

fibrous erionite that are classified as carcinogenic substances. Although in the last 30 years mineral fibres have been the subject of intensive toxicological studies, the mechanisms by which they prompt cyto- and geno-toxic damage *in vivo* are not yet fully understood. Without a clear picture of the role that all the crystal-chemical and physical parameters play in inducing adverse effects, a general quantitative model explaining the toxicity/carcinogenicity of mineral fibres cannot be drawn. With this uncertainty, global issues of social and economic importance cannot be solved. For example, although the toxicity potential of chrysotile asbestos is still highly debated worldwide, this mineral fibre is still used today in "a safe way" in 72% of the world countries. The lack of a quantitative assessment of the toxicity of these materials has another drawback: mineral fibres of unknown toxicity may occur in the natural environment or being in use, causing exposure to the population.

**The general aim of this multidisciplinary project is to fill the gap on the understanding of the bio-chemical interaction of the fibres *in vivo*, by recasting the existing mechanistic models of 'fibre toxicity paradigm'. Only a systematic multidisciplinary approach allows to address the role of critical crystal-chemical-physical parameters that have been poorly investigated or not considered so far to upgrade the existing models of toxicity/carcinogenicity of a mineral fibres.**

Specifically, the FIBRES project is aimed at highlighting the role in inducing toxicity effects of fibres' parameters that have never been considered or deeply investigated to date:

(i) SURFACE IRON SPECIES

Iron is considered to play a role in determining the toxicity of mineral fibres because, when present at the surface, it promotes the release of toxic hydroxyl radicals. In FIBRES, the nature of these iron atoms present at specific surface sites and the mechanism promoting their activity in the different fibre species will be investigated by crystal-chemical, spectroscopic and microscopic methods, combined with free-cell *in vitro* tests for the release of hydroxyl radicals, the most reactive and short-lived oxygen species (ROS).

(ii) BIODURABILITY

In FIBRES, the different kinetic behaviour of mineral fibres during the intracellular dissolution will be assessed quantitatively by *in vitro* acellular tests mimicking the lung's environment. The kinetics and products of dissolution will be investigated by chemical, crystallographic, spectroscopic and microscopic methods. Moreover the potential toxic effects of such compounds will be tested by analysing several biomarkers that play a key-role in the pathways related to cellular damage as adaptive response. So, the biological effects of the fibres, classified as non-biodurable (chrysotile), biodurable (amphibole asbestos), and biodurable but with ion exchange (zeolite erionite), will be carried out using both 2D and 3D *in vitro* physiological relevant biodynamic models of human cells from different target tissues. In 3D *in vitro* cultures, cells are permitted to grow or interact with their surroundings in all three dimensions similar to how they would *in vivo*.

(iii) THE 'TROJAN HORSE-TYPE EFFECT'

Mineral fibres are complex crystal-chemical reservoirs that may release their toxic cargo in the cellular environment during the dissolution process. This mechanism has been observed for nanoparticles for which ion release elicited by the acidic conditions of the lysosomal cellular compartment is responsible for the sequence of events associated with their induced toxicity. Hence, the toxicity potential of mineral fibres must be revised including this effect. To do this, the dissolution and release of toxic metals in simulated lung fluids of natural specimens with different loads will be investigated with chemical and spectroscopic methods. Special attention will be given to the production of ROS and to the cyto- and geno-toxic actions of these fibers.

(iv) INTERFERENCE WITH THE CA-MEDIATED INTRACELLULAR CROSS TALK PROMPTING CELL APOPTOSIS

Apoptosis is a process able to efficiently eliminate damaged cells. Tumor cells have the peculiarity to evade apoptosis and consequently survive and proliferate also in presence of DNA damages, two peculiar hallmarks of cancer. Apoptosis can be activated by several pathways and among them the release of calcium in cytosol plays a crucial role. If the Ca cross talk is deficient, the cycle of apoptotic pathways is interrupted and malignant cells are let free to grow. Zeolite erionite is a peculiar fibre because it possesses ion exchange capacity. In FIBRES, we will evaluate if ion exchange is active during the phagocytosis process of the erionite fibres causing interference with the Ca cross talk. This mechanism will be also investigated by analysing *in vitro* the apoptotic program.

**The FIBRES project will accomplish a comprehensive mineralogical, crystal-chemical-physical and spectroscopic characterization of both the bulk and the surface of mineral fibres. This will be the basis of a quantitative model of bio-chemical interaction of the fibres inducing *in vivo* adverse effects. The model will be verified in an especially developed protocol including 3D *in vitro* toxicity tests, validated by qualified authorities (e.g. the International Agency for the Research on Cancer), and will result in a powerful tool to predict the toxicity/carcinogenicity potential of mineral fibres.**

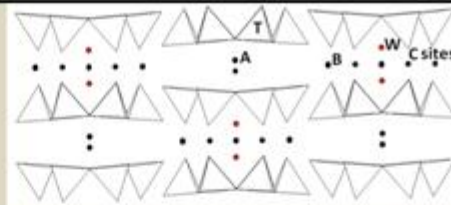
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***2. Detailed description of the project: targets that the project aims to achieve and their significance in terms of advancement of knowledge, state of the art and proposed methodology***

**STATE OF THE ART**

There are more than 400 different species of mineral fibres in nature that can be transported from their pristine occurrence to the urban environment as airborne particulate, through the action of natural or human agents. Among them, amphibole asbestos, chrysotile and fibrous erionite are certainly the most feared ones. Although they share common attributes of being natural silicates, fibrous and carcinogenic (they are all classified by the International Agency for Research on Cancer IARC in Group 1 as Carcinogen for humans: IARC; 2012; Sayan and Mossman, 2017), their crystal-chemical nature and molecular assemblage are indeed very different.

**Amphibole asbestos** are double chain silicates consisting of alternating tetrahedral (T) chains and octahedral band sheets parallel to the (100) plane (Zoltai and Stout, 1987).

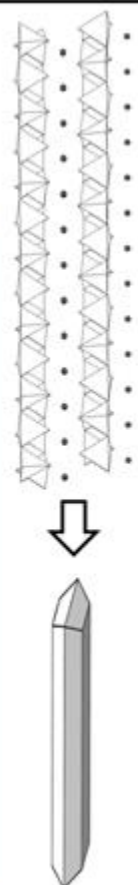


The simplified formula (Hawthorne et al., 2012) is:  $A_{0-1}B_2C_5T_8O_{22}W_2$ . In  $C2/m$  monoclinic forms, the crystallographic sites are:

- A - [12]-fold cavity  $\rightarrow$  ( $\square$ ),  $Na^+$ ,  $K^+$ ,  $Ca^{2+}$ ,  $Li^+$
- B - [8]-fold coordinated  $M(4)$  site  $\rightarrow Na^+$ ,  $Ca^{2+}$ ,  $Mn^{2+}$ ,  $Fe^{2+}$ ,  $Mg^{2+}$
- C - octahedrally coordinated sites  $M(1)$ ,  $M(2)$ ,  $M(3)$   $\rightarrow Mg^{2+}$ ,  $Fe^{2+}$ ,  $Mn^{2+}$ ,  $Al^{3+}$ ,  $Fe^{3+}$ ,  $Mn^{3+}$ ,  $Ti^{4+}$ ,  $Li$
- T - tetrahedrally coordinated  $\rightarrow Si^{4+}$ ,  $Al^{3+}$
- W  $\rightarrow OH^-$ ,  $F^-$ ,  $Cl^-$ ,  $O^{2-}$ .

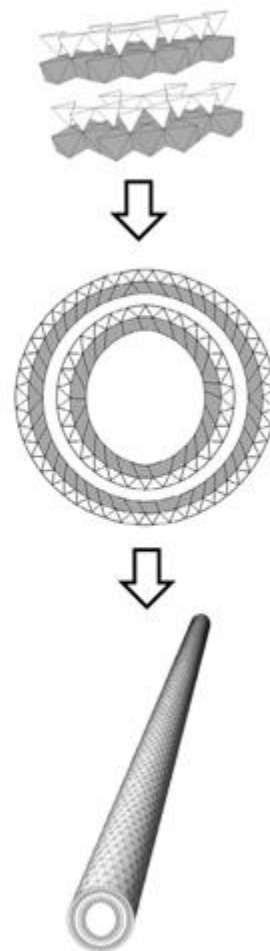
Amphibole asbestos are: actinolite asbestos  $Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$ , amosite  $(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$ , anthophyllite asbestos  $(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$ , crocidolite (fibrous variety of riebeckite)  $Na_2(Fe^{2+},Mg)_3Fe_2^{3+}Si_8O_{22}(OH)_2$  and tremolite asbestos  $Ca_2Mg_5Si_8O_{22}(OH)_2$ .

*The growth of the crystals along the double chains of tetrahedra (white polyhedra) running along the c axis in monoclinic amphiboles is responsible for the fibrous habit.*



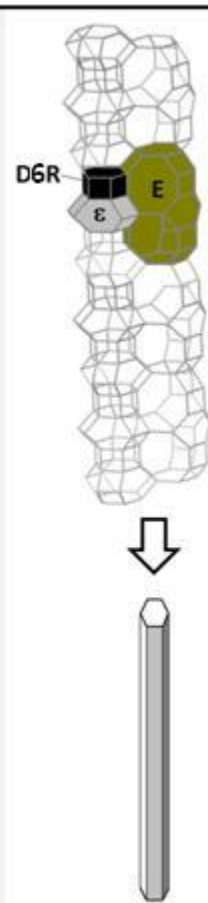
**Chrysotile asbestos** is a layer silicate, ideally characterized by one continuous Si-centred tetrahedral (T) sheet joined to one Mg-centred octahedral (O) sheet. Chrysotile belongs to the serpentine group together with lizardite and antigorite. Although chrysotile is the least abundant of the three serpentine minerals, it accounts for most of the world asbestos production still to date (Ballirano et al., 2017). The ideal chemical formula of serpentine minerals is  $Mg_3(OH)_4Si_2O_5$ .  $Fe^{2+}$  and  $Fe^{3+}$  may substitute for  $Mg^{2+}$  in the O sheet while replacement for  $Si^{+4}$  in the T sheet is infrequent with a preference for  $Al^{3+}$  (O'Hanley and Dyar, 1998). Because of a size misfit between the T and the O sheets, a differential strain occurs between the two sides of the layer (Bailey, 1988). In chrysotile, the strain is released by rolling the TO layer around the fibril axis to end up with a cylindrical (fibrous) structure.

*The rolling of the joined tetrahedral T (white polyhedra) and octahedral O (grey polyhedra) layers determines the fibrous habit of chrysotile.*



**Erionite** is a framework silicate containing a three-dimensional framework of tetrahedra (Wenk and Bulakh, 2004). Environmental exposure to erionite has been linked to the outbreak of malignant mesothelioma (MM) epidemics in several villages of Central Anatolia, Turkey (Baris et al., 1978). Erionite belongs to the so-called ABC-6 family of zeolites (Gottardi and Galli, 1985), whose members are originating from the stacking along the c-axis of layers of secondary building units made of (Si,Al)O<sub>4</sub> tetrahedra, following an ABC scheme. This structure assemblage originates some peculiar extraframework cavities: two double 6-rings (D6R), two cancrinite (ε) cages, and two erionite (23-hedron, E) cages per unit cell. Cancrinite and erionite cages host the extraframework cations (EF) coordinated by several H<sub>2</sub>O molecules (Passaglia et al., 1998). Erionite ideal formula is K<sub>2</sub>(Na, Ca<sub>0.5</sub>)<sub>7</sub>[Al<sub>9</sub>Si<sub>27</sub>O<sub>72</sub>]•28H<sub>2</sub>O (Gottardi and Galli, 1985). There are three different species identified according to the most abundant extra-framework cation: erionite-Na, erionite-K, and erionite-Ca (Passaglia et al., 1998).

*The growth of the crystals along the c axis in erionite is responsible for its fibrous habit. The framework of erionite is shown with the stick model. The D6R, cancrinite (ε) and erionite (E) cages are also evidenced with different shades.*



Because asbestos minerals and fibrous erionite exhibit outstanding physical and technological properties, they have been used since ancient times for a huge number of applications (there are more than 3000 different asbestos-containing items/products). The industrial age of asbestos began in 1805 in Siberia and its massive use (e.g. for the production of cement-asbestos: Gualtieri, 2017) started at the end of 1900 and continues to date. Recognition of the link between occupational exposure to asbestos and specific lung diseases (fibrosis, pleural plaques, carcinoma, malignant mesothelioma) was a relatively late development in occupational epidemiology (Craighead et al., 1982) but is now well documented (see for example Doll, 1955). Widespread acceptance of the association between exposure to asbestos and lung diseases did not occur until epidemiologic studies of cohorts of asbestos workers were published in the 1950s and 1960s (Checkoway et al., 1989).

A number of physicochemical properties of mineral fibres such as size, diameter, surface charge and activity, chemistry (with special attention to iron), ability to generate reactive oxygen species, biopersistence and many more have been implicated in inducing lung diseases (Mossman et al., 1990; Kane, 1996) but their action has not been fully explained, so that a comprehensive model of toxicity/pathogenicity is still missing. As a matter of fact, although in the last three decades, mineral fibres, and especially asbestos/asbestiform minerals, have been the subject of intensive multidisciplinary investigations, the role of the fibres' parameters which induce damage at a molecular scale remain poorly understood. Besides the complexity of the bio-chemical events governing the adverse outcome patterns leading to the malignancies, major difficulties arise from the great variability of the chemistry, molecular arrangement, size, biopersistence and surface reactivity of mineral fibres and cyto- and geno-toxicity data varies greatly with respect to the fibres' parameters (Gualtieri et al., 2017). It is possible to state that many of them (such as iron and biodegradability) are known to have a role and action in inducing adverse effects but a quantitative model has not been drawn yet. Moreover, other parameters and effects have not been considered to date.

Iron is known to play a role in determining the toxicity of mineral fibres (Fubini and Mollo, 1995). During the phagocytosis process, iron present at the fibre/cell interface may promote the release of toxic hydroxyl radicals (•OH), according to the Haber-Weiss cycle (Kamp, 2009):  $Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2^{\bullet-}$  and  $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet OH$  (Fenton reaction). However, a conclusive model for iron has not been developed yet because there is little knowledge about the influence of its chemical environment at the surface of the fibre. To this aim, a key parameter is the nuclearity of the iron site. By definition, iron nuclearity is the number of iron-oxygen-iron bridges, indicated by monomeric (single iron atom, no other iron atoms in the second shell coordination), dimeric (a cluster of two iron atoms, connected by a bridging oxygen atom), trimeric (a cluster of three iron atoms, connected by bridging oxygen atoms), and so on. According to Zecchina et al. (2007), the best candidates to be active sites have a low iron nuclearity but no measurements have been systematically done on iron-containing mineral fibres.



Biodurability is another property of mineral fibres, linked to their different crystal-chemical arrangement, that is known to have a role in inducing adverse effects. Biodurability is one of the two components of biopersistence (the ability of a fibre, or particle in general, to persist in the human body to physico-chemical processes such as dissolution, leaching, breaking, splitting, and to survive physiological clearance: Utembe et al., 2015). The different and complex dissolution behaviour of mineral fibres prompting acute or chronic inflammatory effects *in vivo* must be properly evaluated to assess the actual toxicity/pathogenicity potential of mineral fibres.

Regarding the parameters that have not been explored to date, it should be considered that mineral fibres are complex crystal-chemical reservoirs releasing metals in the intracellular or extracellular environment during the dissolution process. This mechanism, called the 'Trojan horse-type effect', has been observed for nanoparticles (NPs) and is considered responsible for the sequence of events associated with their toxicity (Sabella et al., 2014) but has never been taken into account in the determination of the toxicity/pathogenicity potential of a fibre.

The interference of the mineral fibres with the Ca cross talk prompting cell apoptosis is another unexplored area. Direct or indirect geno-toxic actions of the fibres could facilitate cancerogenic process. Apoptosis is a cell defence mechanism that can be triggered by DNA-damaged cells, in order to prevent neoplastic transformation. Regarding this, cancer cells (by accumulating mutation in several genes involved in apoptosis, questa possiamo ometterla) are able to evade apoptosis and proliferate. Apoptosis is a finely controlled death program and Ca-release from endoplasmic reticulum (ER) into mitochondria and cytosol play a critical role. In this context, BAP1 acts by modulating ER-calcium flux and has recently been involved in environmental carcinogenesis, including mesothelioma. In fact, it was found that reduced levels or mutations of BAP1 gene, leading to a decrease in the Ca-flux, preserve cancer cells from apoptosis (Carbone et al., 2016). Mineral fibres like the zeolite erionite can in principle inhibit the Ca cross talk because they easily exchange this ion in their micropores but such mechanism has never been studied to date.

With the limitations described above, drawing quantitative models that explain the toxicity of mineral fibres has been a pipe dream to date. A part of the scientific community relies upon a simplified mechanistic model called 'fibre toxicity paradigm' (Pott et al., 1994) which is based only upon fibre length L, diameter or width (D), the aspect ratio (L/D) and biopersistence but a more robust comprehensive model which takes into account the complexity of the mineralogy and crystal-chemistry of mineral fibres is needed.

In this grey area, the toxicity/pathogenicity of chrysotile asbestos remains debated and is at the centre of the so-called global chrysotile issue (Carbone et al. 2007): this mineral fibre in the past likely caused thousands of victims in exposed workers and population in most of the European countries but is still used "in a safe way" in several industrialized extra-European countries like Brazil, China, India and Russia. Without a general model for the assessment and prediction of the toxicity of mineral fibres, species of unknown toxicity may be present in the natural or urban environment, possibly causing environmental exposure to the population.

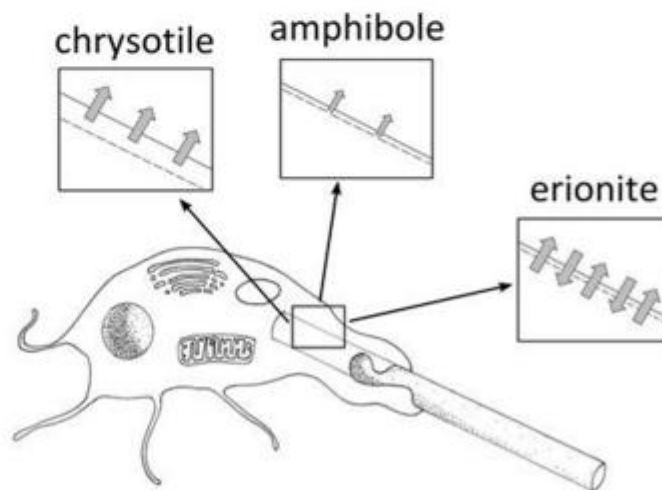
#### TARGETS OF THE PROJECT AND ADVANCEMENT OF THE KNOWLEDGE WITH RESPECT TO THE STATE OF THE ART

**The main target of this multidisciplinary project is to understand how the complex crystal-chemical assemblage forming the structures of mineral fibres determines the bio-chemical interactions that prompt adverse effects *in vivo*.**

A mineralogical, crystal-chemical-physical and spectroscopic characterization of both the bulk and the surface of mineral fibres will be the basis of a revised upgraded model of bio-chemical interaction of the fibres inducing *in vivo* adverse effects which includes parameters that have not been properly considered before or not considered at all. Understanding the role of such crystal-chemical parameters will be of help to update the existing simplified mechanistic models. A systematic multidisciplinary approach will allow us to quantitatively assess the role of these critical parameters and set the basis for a general predictive tool of analysis of the toxicity/cancerogenicity potential. Specifically, the project should clarify the role of the following critical but elusive parameters and effects that promote adverse outcome *in vivo*.

**(i) nature, amount and activity of surface iron species in the different fibres.** To develop a model for the iron-mediated surface production of toxic hydroxyl radicals ( $\cdot\text{OH}$ ), the project will attempt to determine the nature, amount and activity of surface iron species in the different mineral fibres, with a special attention to the nuclearity of the iron sites.

**(ii) biodurability.** In this project, *in vitro* tests will measure dissolution rates of the fibres (biodurability) and use the data for a revised general classification of the fibres based on their biodurability-related effects. The new model will have to classify fibres as (a) non-biodurable (chrysotile asbestos), with fast dissolution rate accompanied by a fast rate of release of their toxic cargo; (b) biodurable (amphibole asbestos), with slow dissolution rate and minor release of their toxic cargo; (c) biodurable, but with ion exchange capacity (zeolite erionite) prompting unpredictable release or adsorption of ions/metals. The **figure** is a sketch of the behaviour of the three fibre types when they undergo phagocytosis by a lung macrophage, the cells designated to the clearance of the fibres: (a) chrysotile dissolves quickly but has a major release of its toxic cargo; (b) amphibole dissolves slowly with a minor release of its toxic cargo; (c) erionite dissolves slowly but is the only fibre able to exchange and capture ions from the surrounding cellular medium.



**(iii) the 'Trojan horse-type effect'**. The concept of the 'Trojan horse-type effect' observed for nanoparticles (NPs) will be applied to mineral fibres, and the toxicity potential of a non-biodurable fibre like chrysotile (case (a) in the classes of biodurability) will be devised so to include the contribution of this effect. In fact, when chrysotile undergoes fast dissolution, it may behave like a carrier that releases its toxic cargo of heavy metals, possibly hosted in the structure, in the lung environment. Oppositely, biodurable amphibole asbestos species slowly release their toxic cargo in the lung environment over a long time period. Fibrous erionite is a special case and requires a dedicated study because it possesses cation exchange capacity (see Ballirano and Cametti, 2015) and may release extraframework metals in the lung environment even if no dissolution occurs.

**(iv) Interference with the Ca cross talk prompting cell apoptosis**. This project is aimed at assessing the cancer self-defence mechanism of 'apoptosis' is influenced by the intracellular chemical reactivity of the engulfed mineral fibres. Specifically, it will be evaluated whether ion exchange is active during the phagocytosis process of the erionite fibres and if there is interference with the Ca cross talk, inhibiting cell apoptosis, so favouring the onset of the malignancies like mesothelioma.

#### SIGNIFICANCE OF THE PROJECT IN TERMS OF ADVANCEMENT OF THE KNOWLEDGE

The outcomes of the project are expected to give outstanding contributions to the advancement of the knowledge in the research field of mineral fibres and their health/environmental impact and risk assessment.

Specifically, the outcomes of the project will lead to a significant improvement of knowledge in the following lines of research:

-comprehension of the role of key mineralogical-chemical-physical parameters and properties of mineral fibres never explored before - like iron surface nuclearity and surface

interacting ability towards cellular components, biodurability, and ion exchange - in inducing toxicity/pathogenicity effects in vivo;  
-understanding the nature of the parameters and the effects that play a synergetic role in determining the potential toxicity/pathogenicity of mineral fibres, to be used to revise existing quantitative predictive models;  
-obtaining all the elements to assess the actual toxicity of chrysotile asbestos, especially in comparison with amphibole asbestos, necessary to take a decision about its global ban;  
-setting up of a standard procedure of analysis to predict the potential toxicity of mineral fibres that are not yet classified;  
-setting up of a standard experimental procedure for the preparation of mineral fibres to be tested in quantitative in vitro toxicity tests;  
-understanding how mineralogical-chemical-physical parameters and properties of mineral fibres - like iron and other metals ('Trojan horse effect'), biodurability, and ion exchange - affect the quantitative results of acellular and cellular toxicity/pathogenicity tests in vitro;  
-creating a standard experimental procedure for 3D in vitro toxicity tests for mineral fibres;  
-improving the comprehension of the biochemical mechanisms leading to carcinogenesis, opening new ways for the treatment of people exposed to asbestos related lung diseases;  
-providing quantitative models to the environmental agencies to develop strategies and procedures for risk control/prevention/mitigation of the environmental exposure to toxic/carcinogenic mineral fibres.

#### CONSISTENCY OF THE OBJECTIVES AND ADVANCEMENT OF THE KNOWLEDGE OF THE PROJECT WITH THE RESEARCH AND INNOVATION STRATEGIES AT NATIONAL AND EUROPEAN LEVEL

The objectives and advancement of the knowledge of the project are consistent with the:

National Research Program PNR 2015-2020 - Miur  
Priority specialization Area: Health (Priorità salute).

#### National Smart Specialization Strategy

The goals of the National Smart Specialization Strategy as Systems at high potential and growth, within the macro-objective Innovation of the industrial processes in the health system (Innovazione nei processi industriali in sanità, L'industria della salute e del benessere", sezione a. Diagnosi precoce e diagnostica in vivo ed in vitro, Traiettorie di evoluzione: biomarcatori per il monitoraggio della salute) aimed at upgrading procedures and methods for the diagnosis and monitoring of health and wellbeing of the population, with a special attention to the biomarkers relative to the diagnosis, prognosis and monitoring of the health.

#### European challenges (Horizon 2020)

First macro-objective: Health, demographic change and wellbeing aimed at personalising health and care with a Research and Innovation to improve our understanding of the causes and mechanisms underlying health, disease and improve our ability to monitor health and to prevent, detect, treat and manage disease. The actual and future challenge is to convert actual aid-oriented medicine to a predictive medicine. This new concept in medicine and biology is related to the evolving concept of health that should be oriented to a sustainable holistic, interdisciplinary approach.

#### PROPOSED METHODOLOGIES

The multidisciplinary quantitative approach adopted by the project to assess the role of the crystal-chemical and physical parameters influencing the toxicity/cancerogenicity potential of mineral fibres will take advantage of different experimental methodologies.

To study (i) SURFACE IRON AND ITS ACTIVITY, iron crystal-chemistry of the fibres will be initially investigated using bulk methods like electron probe microanalysis (EPMA) for the quantitative determination of iron content, X-ray absorption spectroscopy XAS (XANES and EXAFS) at the iron edge to be done at the synchrotron facilities, Mössbauer spectroscopy to study iron oxidation state and local coordination. Fourier-Transform Infra-Red (FTIR) and Raman spectroscopies will be applied in the attempt to complete the information about iron nuclearity. The structure models of the mineral fibres - necessary to better understand the position of iron in the crystal lattice - will be determined by single crystal (XRSC) and powder X-ray diffraction (XRPD) at lab and synchrotron facilities. Surface sensitive spectroscopic methods will then be applied: X-ray photoelectron spectroscopy (XPS) supported by Electron paramagnetic resonance (EPR) for the determination of the reactive oxygen species (ROS), mostly hydroxyl radicals, and both EPR and Fluorescence spectroscopy to assess the interacting ability of the surface. The nature of iron-containing impurities at the surface of the fibres will be observed with transmission electron microscopy (TEM) accompanied by electron energy loss spectroscopy (EELS) as chemical probe.

The study of (ii) the BIODURABILITY will be conducted through in vitro acellular tests with the fibres in contact with simulated lung fluid (SLF) (De Meringo et al., 1994) mimicking both the extracellular (pH=7.4 and ascorbic acid in micromole concentration) and intracellular conditions (phago-lysosome environment buffered at pH=4). Specific surface areas will be accurately determined to normalize the dissolution rates. The kinetics of element dissolution in suspension will be followed by monitoring the element concentration with atomic absorption spectroscopy (AAS) and mass spectrometry (ICP-MS). The structural modifications of the mineral fibres during the dissolution process will be monitored using XRPD, supported by micro-Raman studies. The modification of the shape of the fibres will be observed with TEM.

The study of the (III) 'TROIJAN HORSE-TYPE EFFECT' will be conducted on natural specimens with different toxic loads (especially Fe, V, Cr, Mn, Ni for chrysotile and amphiboles) dissolved using the SLF described above to reproduce the lung environment. The rate of ion release will be monitored by determining the ion concentration as a function of time by EPMA, AAS and ICP-MS analyses. The surface interacting ability of the fibres towards specific target proteins and cellular components will be assessed by EPR.

The possible (iv) INTERFERENCE OF FIBROUS ERIONITE WITH THE CA CROSS TALK will be investigated with ion exchange experiments on selected fibrous erionite samples, mimicking the intracellular environment of the phago-lysosome (see above). The structure models of the exchanged (Ca-, Na-, K-) forms will be studied with XRSC and XRPD and supported by micro-Raman data. The measurement of the zeta potential (surface charge) of the investigated fibres will help to understand the chemical gradients prompting the ion exchange in vivo. Ion exchange will be monitored in situ when the fibres are in contact with cell cultures during the process of phagocytosis with TEM/EELS and XRF mapping at a synchrotron facility (see an example in Pascolo et al., 2016).

To verify the models in vivo, the study of the parameters described above will be supported by in vitro geno- and cyto-toxicity tests and in vivo tests. In vitro genotoxicity tests will detect the potential damage induced by asbestos fibres on genetic material in the cells through interactions with the DNA sequence and structure. Induced genotoxicity can be classified as primary genotoxicity, the genetic damage induced by asbestos fibres themselves, and secondary genotoxicity that implies involvement of inflammatory cells resulting in the oxidative damage of DNA by ROS. For in vitro assays, the selected mineral fibres will be administered at specific doses and time points to different human cell lines. For the direct genotoxicity investigation, various screening will be used (micronucleus assay, the COMET assay, DNA strand breakage and response to different biochemical stimuli, assessment of miRNA expression profiles) in the above mentioned panel of human cell cultures. The indirect genotoxicity tests will be assessed by fluorescent immunostaining, in terms of BAP1 localization, in primary human mesothelial cells and normal fibroblasts. The biological activity of iron in the different iron-rich fibres will be monitored in vitro with physiologically-relevant 3D models of human normal cells from different target tissues. In 3D in vitro cultures, cells are permitted to grow or interact with their surroundings in all three dimensions in specially developed bioreactors. Unlike 2D environments, the 3D cell culture allows cells to grow in all directions, similar to how they would in vivo.

The cyto- and geno-toxic action of the different fibres and of the toxic metals released during the dissolution will be determined in in vitro in 2D cell cultures and 3D tissue models through toxicity and metabolic tests. Activation of inflammatory/apoptotic pathways will be thoroughly investigated as well. To this aim, because quantitative toxicological studies require to control the size and diameter of the fibres, a novel analytical protocol will be devised and optimized for the preparation of samples as well as in the interpretation of experimental studies.

The availability of the 3D cellular system permits to study the effects of the fibres on several Ca-dependent process such as survival, proliferation and senescence. Furthermore, the possible unbalance of Ca signaling (influx or release from intracellular stores) in living cells challenged with the toxic fibres will be evaluated by confocal microscopy/fluorimetric analyses by use of specific Ca sensitive ratiometric and non-ratiometric dyes.

Moreover, in vivo studies of the tissues from human organs will be accomplished by collecting the immunohistochemistry response with the protein assessment of apoptosis such as caspase-1, -3 and -9, and the different expression rate of BAP1 gene.

The results of the **FIBRES project** will be elaborated and discussed in synergy by all participants to this multidisciplinary project, including a biomedical and epidemiological staff. **The final goal is to revise and upgrade the existing models which describe the toxicity/pathogenicity of mineral fibres in a quantitative way, classify the existing species and predict the behaviour of unclassified fibres.** The developed models will be submitted for **validation to qualified international authorities.**

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### ***3. Project development, with identification of the role of each research unit with regards to expected targets, and related modalities of integration and collaboration***

### **MAIN TARGET OF FIBRES PROJECT**

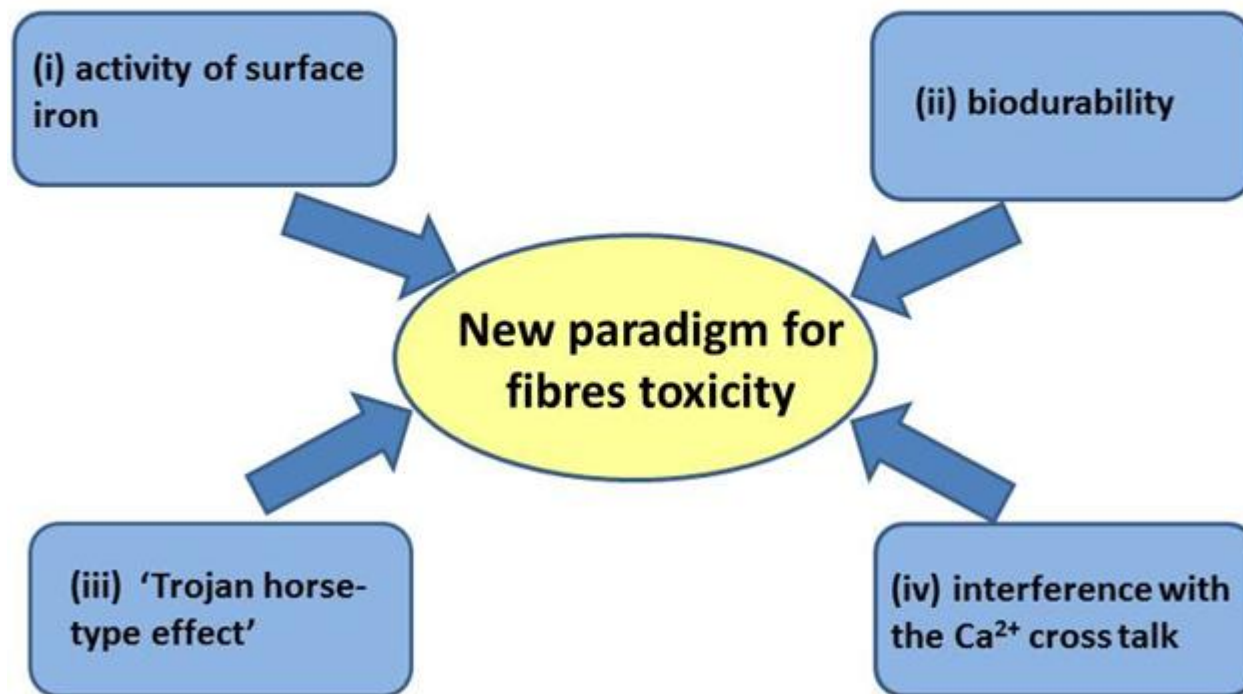
**To amend the existing mechanistic models of 'fibre toxicity paradigm' including the role of crystal-chemical parameters that were not considered before in inducing toxicity/carcinogenicity**

### **FINAL AIM OF FIBRES PROJECT**

**To set the basis of a quantitative model of bio-chemical interaction of the fibres inducing *in vivo* adverse effects.**

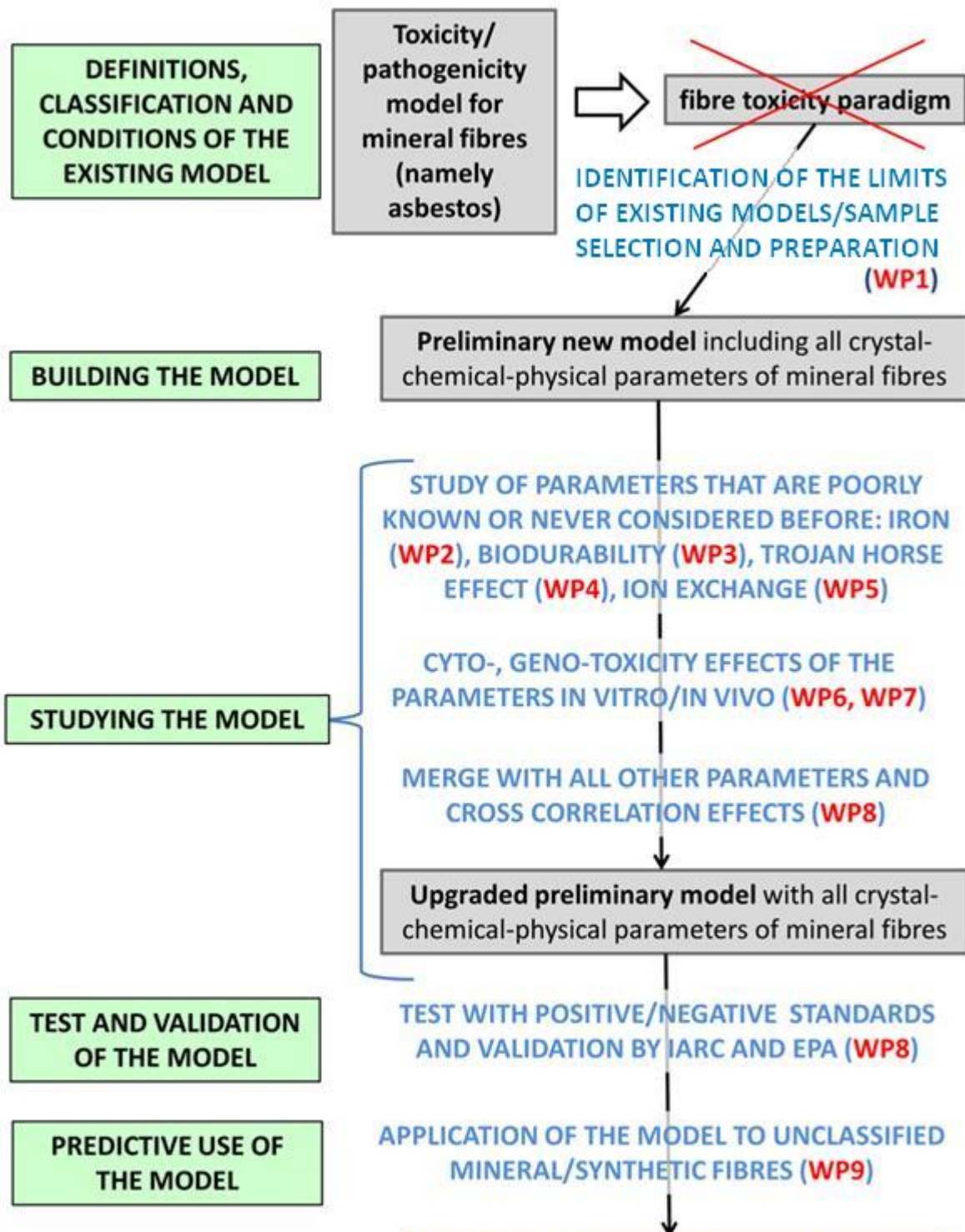
The main target of the project is to revise the existing models of 'fibre toxicity paradigm' to include the role of crystal-chemical-physical parameters of mineral fibres that have never been considered before. The parameters and effects contributing to the toxicity/pathogenicity of mineral fibres that will be investigated are: (i) ACTIVITY OF SURFACE IRON; (ii) BIODURABILITY; (iii) 'TROIJAN HORSE-TYPE EFFECT'; (iv) INTERFERENCE WITH THE CA INTRACELLULAR CROSS TALK.

## Critical parameters affecting fibres toxicity



The understanding of the role of these parameters permits to upgrade the existing models of toxicity/pathogenicity of mineral fibres. The developed models will be discussed and validated with national and international entities like the Istituto Superiore di sanità (ISS), the International Agency for the Research on Cancer (IARC) and by the US Environmental Protection Agency (EPA). The models will be finally applied to mineral fibres that are not classified to date so to determine their toxicity/pathogenicity.

The plan of activities of the project is summarized in the following flow chart.





## New fibre toxicity paradigm

In the following section illustrates the FIBRES WORK PLAN distributed over a series of specific PACKAGES.

### RESEARCH UNITS - LEGEND

**UNIMORE: University of Modena and Reggio Emilia (P.I. A.Gualtieri)**

**SAPIENZA: University of Roma La Sapienza (L.R. P. Ballirano)**

**UNIGE: University of Genova (L.R. A.M. Bassi)**

**UNIPI: University of Pisa (L.R. S. Raneri UNDER 40)**

**UNIURB: University of Urbino Carlo Bo (L.R. M.F. Ottaviani )**

**UNIVPM: University Politecnica delle Marche (L.R. A. Procopio)**

**WORK PACKAGE (WP) 1: BUILDING OF THE MODELS, SELECTION AND PRELIMINARY CHARACTERIZATION OF THE MINERAL FIBRES.**

Task 1.1 - Definition of the state of the art, classification of the existing models, definition of the assumptions and adaptation of the new comprehensive model to the old ones, taking into account all the toxicity/pathogenicity inducing parameters and effects of the fibres (UNIMORE);

Task 1.2 - Search and selection of the mineral fibres: industrial chrysotile asbestos samples (Brazil, Russia), industrial amphibole asbestos samples, fibrous erionite from the US and Turkey, various natural and synthetic fibrous zeolites, fibrous glaucophane from the US, fibrous antigorite from New Caledonia (UNIMORE);

Task 1.3 - Preliminary mineralogical and chemical characterization of the materials.

Task 1.3.1 - Determination of the specific surface (BET) and zeta potential (UNIMORE);

Task 1.3.2 - X-ray Powder Diffraction (XRPD) (SAPIENZA);

Task 1.3.3 - X-ray single crystal Diffraction (XRSC) and Micro-Raman (UNIPI);

Task 1.3.4 - FTIR and determination of morphometric parameters using FEG-SEM/EDS (UNIURB).

**WORK PACKAGE (WP) 2: STUDY OF THE ACTIVITY OF SURFACE IRON (I).**

Task 2.1 - Characterization of bulk iron crystal chemistry.

Task 2.1.1 - XAS (XANES and EXAFS) at a synchrotron facility (UNIMORE);

Task 2.1.2 - Mössbauer spectroscopy and XRPD (SAPIENZA);

Task 2.1.3 - EPR and FTIR (UNIURB);

Task 2.1.4 - XRSC (UNIPI).

Task 2.2 - Application of surface sensitive methods to study iron crystal chemistry.

Task 2.2.1 - XPS (UNIMORE);

Task 2.2.2 - EPR for the determination of the reactive oxygen species ROS; EPR and Fluorescence spectroscopy to assess the reactivity of the surface (UNIURB);

Task 2.2.3 - Study of iron-containing impurities at the surface of the fibres by TEM/EELS (SAPIENZA).

#### WORK PACKAGE (WP) 3: BIODURABILITY (II).

Task 3.1 - Cell-free in vitro tests mimicking the conditions inside a phago-lysosome with a simulated lung fluid (SLF) with atomic absorption spectroscopy (AAS) and mass spectrometry (ICP-MS) (UNIMORE);

Task 3.2 - Determination of the structure and microstructure variations of the mineral fibres during the dissolution process.

Task 3.2.1 - XRPD (SAPIENZA);

Task 3.2.2 - XRSC and Micro-Raman study (UNIPI);

Task 3.2.3 - TEM study (SAPIENZA).

#### WORK PACKAGE (WP) 4: THE 'TROJAN HORSE-TYPE EFFECT' (III).

Task 4.1 - Study of the release of toxic elements from natural specimens, dissolved using the SLF to reproduce the intracellular environment.

Task 4.1.1 - EPMA, AAS and ICP-MS (SAPIENZA);

Task 4.1.2 - Surface activity and production of ROS by EPR (UNIURB).

#### WORK PACKAGE (WP) 5: INTERFERENCE WITH THE CA CROSS TALK (IV).

Task 5.1 - Structure refinement of selected fibrous zeolites (erionite and ferrierite) and their Ca-, Na-, K-exchanged forms in SLF, mimicking the intracellular environment and the cross talk phenomenon.

Task 5.1.1 - XRPD (SAPIENZA);

Task 5.1.2 - XRSC and micro-Raman (UNIPI);

Task 5.2 - Preparation of thin sections of selected fibrous zeolites (erionite and ferrierite) inside macrophage cells' cultures to follow the process of phagocytosis and Ca cross talk with time using TEM/EELS (UNIMORE).

#### WORK PACKAGE (WP) 6: IN VITRO CYTO-TOXICITY TEST LINES.

Task 6.1 - Setting up of a novel analytical protocol for the preparation of fibre samples for quantitative in vitro tests based on nano-drop deposition techniques already set up for extremely diluted samples (UNIURB);

Task 6.2 - Study of the impact of the toxic elements released during the dissolution process in in vitro in 3D tissue models through toxicity and metabolic tests (UNIGE);

Task 6.3 - Study of the unbalance of Ca signaling in living cells challenged with the toxic fibres evaluated by confocal microscopy/fluorimetric analyses by use of specific Ca sensitive dyes (UNIGE);

Task 6.4 - Evaluation of biological potential impact of chronic exposure to the fibres (7-30 days) on several 3D in vitro human models with endpoints to be analysed: i) Viability index, healthy state, proliferation index and cellular bioenergetics; ii) gene and/or protein expression analysis and specific biomarker activities related to inflammation, oxidative stress, heat shock protein expressions, GHS/GSSG ratio, enzymatic antioxidant activity; cell damage signaling; apoptosis; autophagy; fibrosis. Spectrometric/fluorimetric, HPLC, molecular biology and confocal microscopy techniques (UNIGE).

#### WORK PACKAGE (WP) 7: IN VITRO AND IN VIVO GENO-TOXICITY TESTS.

Task 7.1 - Direct genotoxicity investigation: Micronucleus (MN) assay, COMET assay, DNA-damage response. BAP1 gene expression perturbation by fluorescent immunostaining. Subcellular localization of BAP1 protein by immune electron microscopy. Assays with human cell cultures: MeT5A and BEAS 2B (SV40-immortalized mesothelial and bronchial epithelial cells), A549 (non-small cell lung carcinoma (NSCLC)-derived cell line), THP-1 (monocytic cell line as model to study "frustrated phagocytosis"), and primary human mesothelial cells and normal fibroblasts (UNIVPM).

Task 7.2 - Toxicogenomic approaches expected to identify unique gene expression profiles: alteration of the miRNAs expression profile in both BeWo cell and HTR8/SvNeo (mimicking placental/foetal barrier) in primary human mesothelial cells and in normal fibroblasts, in light of its possible use as biomarkers in occupational health studies (UNIVPM).

Task 7.2.1 - Indirect genotoxicity analysis: pyroptosis (inflammasome activation by caspase-1 Colorimetric Assay), glutathione depletion by spectrophotometric assay, oxidative stress via the depletion of glutathione (GSH), and other antioxidant defences (UNIVPM).

Task 7.3 - In vivo studies of human organs: human tissues (obtained from lungs, mesothelial, peritonea and placenta) will be collected and divided in case and control groups (UNIVPM).

Task 7.3.1 - immunohistochemistry (protein assessment of apoptosis such as caspase- 1,-3 and -9, expression rate of BAP1 gene) (UNIVPM).

Task 7.3.2 - TEM and SEM for morphological investigation and occurrence of asbestos bodies. Immuno electron microscopy with subcellular localization of BAP1 protein (UNIVPM).

Task 7.3.3 - Molecular analysis to detect the assessment of miRNAs expression profiles in the above mentioned case and control tissues (UNIVPM).

**WORK PACKAGE (WP) 8: TEST AND VALIDATION OF THE MODEL.**

Task 8.1 - Set up of the new models with the existing models for all the other crystal-chemical-physical parameters of mineral fibres and evaluation of the cross-correlations to create a comprehensive tool of analysis for the prediction of the toxicity/pathogenicity potential of mineral fibres.

Task 8.1.1 - The mineralogical aspects (UNIMORE);

Task 8.1.2 - The cyto-toxic aspects (UNIGE);

Task 8.1.3 - The geno-toxic and in vivo aspects (UNIVPM);

Task 8.2 - Testing of the revised developed model with positive toxic/carcinogenic substances (e.g. crocidolite) and negative standards (e.g. wollastonite) (ALL RESEARCH UNITS);

Task 8.3 - Discussion, revision and validation of the models by competent national and international authorities like ISS, IARC and US EPA (UNIMORE).

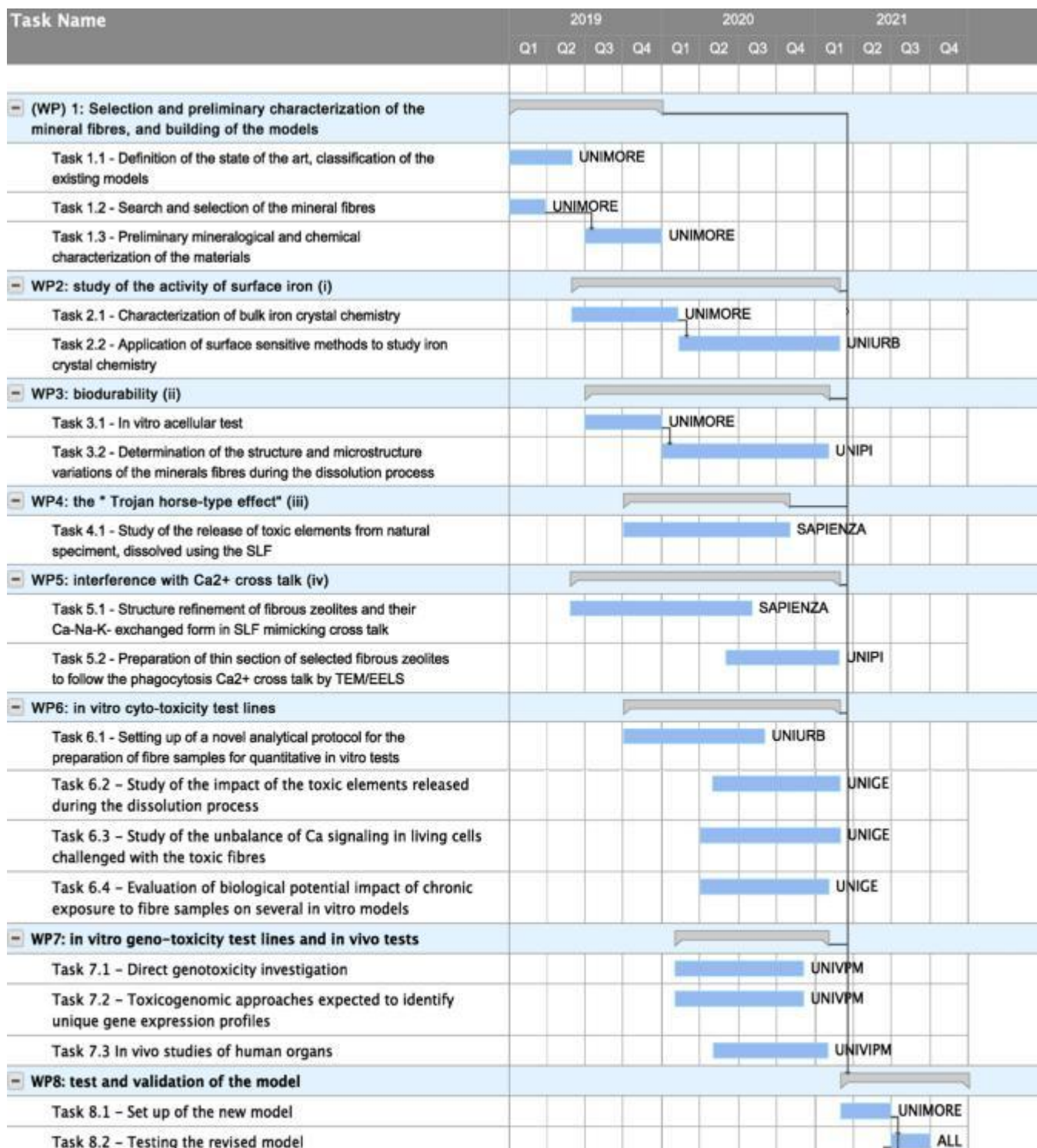
**WORK PACKAGE (WP) 9: USE OF THE MODEL.**

Task 9.1 - Application of the model to unclassified mineral fibres (UNIMORE);

Task 9.2 - Development of a national network of laboratories for the analysis and determination of the fibre potential toxicity/pathogenicity and relative software tools (UNIMORE);

Task 9.3 - Dissemination of the results of the project (publications, conferences/workshops/events, website) to maximize the visibility of the project outputs and outcomes, and share the outcomes with stakeholders, relevant institutions, and health/environmental organisations (ALL RESEARCH UNITS).

The GANTT time sheet of the project is shown below. Only the research unit responsible for each Task is reported.

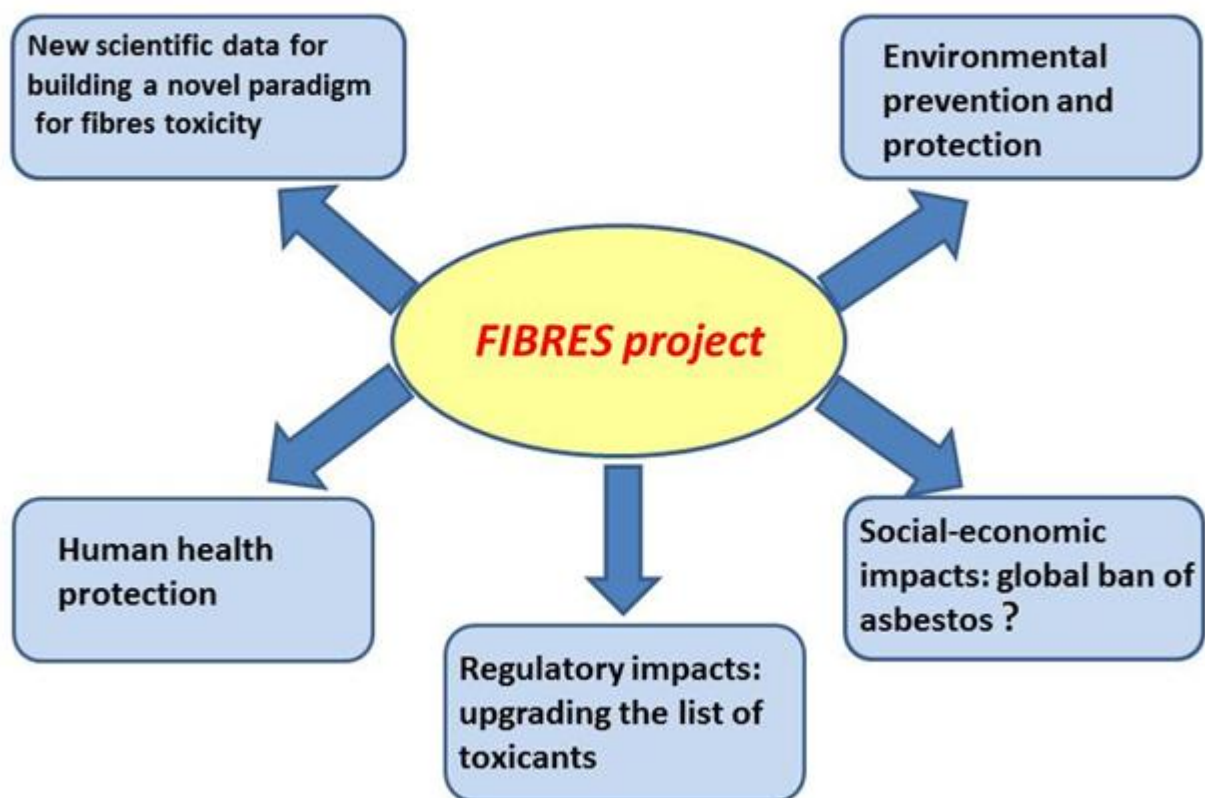


	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
	2019				2020				2021				
Task 8.3 – Discussion and revision of the model													ALL
<b>WP9: use of the model</b>													
Task 9.1 – Application of the model to unclassified mineral fibres													UNIMORE
Task 9.2 – Development of a national network of laboratories for the analysis and determination of the fibre potential toxicity													UNIMORE
Task 9.3 – Dissemination of the results of the project													ALL

#### 4. Possible application potentialities and scientific and/or technological and/or social and/or economic impact of the project

The project FIBRES has several POTENTIAL APPLICATIONS and scientific, social and economic IMPACTS.

### Potential applications and impacts of **FIBRES**



**SCIENTIFIC IMPACTS**

- revision of the existing models describing the role of the mineralogical-chemical-physical parameters and properties of mineral fibres, biodurability, and ion exchange in inducing toxicity/pathogenicity effects in vivo;
- introduction of the quantitative models to bio-medical authorities to support the understanding of the biochemical mechanisms leading to carcinogenesis, potentially opening new ways for the treatment of people exposed to asbestos related lung diseases;
- revision and optimization of the experimental protocols for the sample preparation of the fibres to be used for the quantitative toxicity tests. These tests require a selection and control of the fibre aspect ratio (size and width) to make data comparable among various species. In particular, the tests need to focus on the number and textures of fibres and not just on the weight, as the apparent local density of mineral fibres in a deposition can be considerably different;
- application and validation of the in vitro quantitative acellular and cellular toxicity/pathogenicity tests to the mineral fibres including the 'Trojan horse effect' and other effects studied in this project;
- application of innovative 3D in vitro toxicity assays to the mineral fibres;
- Training of 1 young under 40 Researcher to become a leading scientist in this field of research, 1 PhD, and 6 grant contractors.

**SOCIAL-HEALTH-ENVIRONMENTAL IMPACTS**

- modelling a priori the potential toxicity of unclassified mineral fibres prompts proper plans of risk abatement and prevention;
- the revised and upgraded models developed for natural mineral fibres and the information provided by the multidisciplinary approach adopted by FIBRES can also be used to upgrade the existing models to assess the toxicity potential of synthetic ('man-made') mineral fibres.

**SOCIAL-ENVIRONMENTAL-REGULATORY IMPACTS**

- the final models will be disseminated to academic, public (environmental regional agencies such as ARPAE, AUSL and others) or private entities to develop tools for risk control and environmental prevention from the exposure to mineral fibres;
- the predictive models of toxicity/pathogenicity can also be a support for the accreditation procedures of natural/synthetic raw materials, within the REACH (Regulation, Evaluation, Authorization and Restriction of Chemical Substances) regulation of the European Union;
- the predictive models will be introduced to the most distinguished national and international authority in cancer research, like Istituto Superiore di Sanità (ISS) and the International Agency for the Research on Cancer (IARC). IARC is aimed at discovering the causes of cancer, so that preventive measures may be adopted. Hence, IARC may be interested in adopting the protocol of analysis to assess the toxicity/pathogenicity potential as preliminary assessment step in their standard procedures for the classification of substances based on their cancer-inducing potential;
- the predictive models will be introduced to one of the most distinguished authorities in environmental protection in the United States, the US Environmental Protection Agency (EPA) to be merged with their standard procedures for the assessment of toxicity and environmental risk of mineral substances and promote actions for the detection of the natural occurrences of potentially unregulated/unclassified toxic fibres that may be sources of exposure for the population.

**SOCIAL-ECONOMIC IMPACTS**

- FIBRES will contribute to finally assess the actual toxicity of chrysotile asbestos, that has not been globally banned to date. In case it is demonstrated that the toxicity of chrysotile asbestos is comparable to that of amphibole fibres, this result would support the global ban of chrysotile asbestos in the world. This ban would have an enormous social impact on millions of people around the world (72% of the countries worldwide are still mining, manufacturing, using and exporting chrysotile 'in a safe way') that would no longer be exposed to chrysotile asbestos fibres;
- if the modelling of the chrysotile fibre confirms its potential toxicity, even this mineral substance will be included in the list of toxicants of the Rotterdam Convention, which imposes labelling of the products containing toxic substances. This has a huge social and economic impact for the global market import/export as there will be no more risk of illegal/unaware import of chrysotile asbestos containing products in the countries (mostly Europe) that have banned it from foreign countries still marketing them (e.g. Brazil, China, and Russia).

**5. Costs and fundings, for each research unit (automatically calculated)**

<b>n° Associated or principal investigator</b>	<b>Total cost (euro)</b>	<b>Co-funding (item A.1) (euro)</b>	<b>MIUR funding (other items) (euro)</b>
1. GUALTIERI Alessandro	169.500	14.563	154.937
2. RANERI Simona	85.000	2.246	82.754
3. BALLIRANO Paolo	100.000	10.135	89.865
4. OTTAVIANI Maria Francesca	100.000	11.237	88.763
5. BASSI Anna Maria	115.000	11.628	103.372
6. PROCOPIO Antonio Domenico	100.000	5.478	94.522
<b>Total</b>	<b>669.500</b>	<b>55.287</b>	<b>614.213</b>

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## **B.2**

### **1. PI's Curriculum Vitae**

#### Education and career:

- Degree in Geology (March 1991) at the University of Modena (110/110 cum laude);
- PhD in Mineralogy and Crystallography at the Dipartimento di Scienze della Terra (1992-1995) University of Modena. Spent part of the PhD formation at the National Synchrotron Light Source (NSLS, BNL) in Brookhaven (NY, USA) and at the Chemistry Department of The Stony Brook University (NY, USA);
- Appointment of University Researcher (November 1994) at the Dipartimento di Scienze della Terra, The University of Modena;
- Appointment of Associate Professor (October 2000) of Mineralogy at the Dipartimento di Scienze della Terra, The University of Modena and R.E.;
- Appointment of Full Professor of Mineralogy (February 2005) at the Dipartimento di Scienze Chimiche e Geologiche, The University of Modena and R.E.

#### Relevant professional and institutional assignments/activities:

- Member of the Scientific Committee of the Italian experimental beamline BM08 at the Synchrotron Radiation Facility, Grenoble (FR) 2000-2003;
- Member of the European Powder Diffraction Committee (EPDIC) 2005-2007.
- Member of the Commission on Crystallographic Computing of the International Union of Crystallography (IUCr) 2003-2005 and 2006-2009;
- Associated Editor of the of the scientific "American Mineralogist" 2001-2005;
- Member of the Scientific Committee CERIC-ERIC Synchrotron Facility Trieste, AREA Science Park Trieste (Basovizza), Italy 2015-now.
- Member or president of committees for the selection procedure of full professorship (2), associate professorship (4), assistant professorship/researcher (2), and PhD final exams (10).

#### Research activity:

Since 1992, the P.I. has been involved in basic and applied research on asbestos and mineral fibres, quantitative determination in massive and airborne matrices and their crystal chemical characterization with lab instrumentation and synchrotron radiation. A long term research project has been conducted on the thermal transformation of asbestos containing wastes, recycling of the secondary raw material (end of waste) and the solution of the asbestos problem. Research activity has now shifted to the crystal chemical characterization of mineral fibres of social and economic and the mechanisms producing adverse effects in vivo. Along this research line, important results were accomplished from the study of the mineral fibres in contact with cell cultures (in vitro tests) and in vivo (within the lungs of rats, with a special attention to the mechanism of formation of asbestos bodies). Based on a multidisciplinary approach, the

outcome of this research activity has been the development of a preliminary predictive model to assess the toxicity/pathogenicity of mineral fibres. Monitoring of asbestos in the working and life environment (e.g. landfills) and contribution to the development of environmental protection and prevention plans is another important line of research followed in the last decade.

Experimental activity has been conducted at synchrotron (RAL and Diamond, UK; ESRF, France; Elettra, Italy) and neutron (ISIS, UK; ILL, France) facilities. Recently, the P.I. coordinated a novel experiment of nanodiffraction on the mineral fibres erionite and crocidolite: Experiment 401100 "Nanodiffraction on mineral fibres", ID11 beamline (local contact Giacobbe C.), ESRF, Grenoble (France), 19-23/09/17.

The research activities on mineral fibres and their thermal transformation have been funded by National/International research projects (PRIN and local grants) such as 2004-2007: "Il monitoraggio dell'amianto nell'ambiente di vita e di lavoro per ottimizzarne la neutralizzazione ed il riciclaggio", Fondazione Cassa di Risparmio di Modena, and private companies under financed research contracts (e.g. Zetadi s.r.l).

Recent activity as visiting professor:

- Visiting Professor at the Centre of Excellence Telč (Czech Republic) May 2014 for research activity on the kinetics of setting of magnesium phosphate cements;
- Visiting Professor at ARPA Aosta (Saint-Christophe, Valle d'Aosta) for research in the field of asbestos minerals May 2014;
- Visiting Professor at the Institut für Geowissenschaften, Friedrich-Schiller Universität Jena (Germany), May 2016.

Recent relevant Congress/Editorial activities:

- Convenor of the session "Medical and Environmental Mineralogy" (S. Fiore, R. Giere, A.F. Gualtieri, L. Posfai). EMC2 European Mineralogical Conference, Frankfurt / Main Germany 2-6/09/2012;
- Chair of the Workshop "Corso di aggiornamento teorico-pratico sull'uso della diffrazione di raggi X da polveri nella scienza dei materiali ed applicazioni industriali". Centro Interdipartimentale Grandi Strumenti, Università degli studi di Modena e Reggio Emilia, Modena (Italy), 19/06/2013;
- Chair of the session "SILS-AIC joint session" FisMat 2013 Italian National Conference on Condensed Matter Physics Politecnico di Milano, Milano (Italy), 13/09/2013;
- Chair of the session EM6 "Inorganic fibres, biosphere, and risk assessment". Boardroom 4,. 21st General Meeting of IMA South Africa 2014, Sandton, Johannesburg, Gauteng, South Africa. 01-05/09/2014;
- Chair of the session MS6. Crystal chemistry of inorganic compounds for the understanding of their properties and stability. 44° Italian Crystallographic Association (AIC) meeting, Vercelli (Italy), 14-18/09/2015;
- Chair of the Session S26 Mineral-Hazards. The environmental and human health problem represented by raw and man-processed mineral phases. Emc2 2nd European Mineralogical Conference. Rimini (Italy), 15/09/2016;
- Chair of the European Mineralogical Union School "Mineral fibres: crystal chemistry, chemical-physical properties, biological interaction and toxicity" Modena (Italy) June 19-23, 2017;
- Editor of the EUROPEAN MINERALOGICAL UNION NOTES IN MINERALOGY (2017) Volume 18 MINERAL FIBRES: CRYSTAL CHEMISTRY, CHEMICAL-PHYSICAL PROPERTIES, BIOLOGICAL INTERACTION AND TOXICITY, pp. 536;
- Convenor of the session P12. Geomaterials and their likes: from Nature to technology and manufacturing. M. Mercurio, G. Eramo, C. Zanelli, A.F. Gualtieri. SIMP-SGI-AIV-SoGei Congress 2017 'Geosciences: a tool in a changing world'. Pisa, 4-6/09/2017.

Teaching duties:

- The teaching activity embraces various geology courses (e.g., Natural Raw Materials, first/second level degree of Geology 2002-2017; Applied Crystallography, second level degree of Geology 2004-2017; Mineralogy II, first level degree of Geology 2009-2017);
- Past President of the Degree Council of Geology courses of the University of Modena and R.E. 2008-2012;
  - Supervisor/co-supervisor of more than 100 first/second level degree and PhD theses.

Summary of bibliographic data:

- Total Nr. Citations (Scopus) 3819 (20 march 2018);
- 279 papers on National/International scientific journals;
- 5 patents (3 Italian patents and 2 European patents);
- 154 Oral presentation at International/National Conferences/Congresses;
- 85 poster presentation at International/National Conferences/Congresses;
- 84 seminars in Italy and abroad.

## 1.a National and international grants (as Principal Investigator)

The National grants that have been assigned, on the basis of peer review process, for research activities on mineral fibres and asbestos to the Principal Investigator as Scientific Responsible:

-Fondazione Cassa di Risparmio di Modena (2004) for the project "Il monitoraggio dell'amianto nell'ambiente di vita e di lavoro per ottimizzarne la neutralizzazione ed il riciclaggio" (3 years - 120.000,00 euro).

-FAR2017 (2017) Inter-department research project "Fibre potential toxicity Index (FPTI)" (2 years - 70.000,00 euro).

## 1.b National and international acknowledgments

### ASSOCIATION BOARDSHIP AND COMMITTEES

-Member of the Committee "STRUMENTAZIONE e CALCOLO" - Associazione Italiana di Cristallografia (AIC)(2000-2002);

-Member of the Board of "Associazione Italiana Zeoliti" (2002-2004);

-Member of the Commission on Crystallographic Computing dell'International Union of Crystallography (IUCr) (2003-2009);

-Consultant of the Commission on Crystallographic Computing dell'International Union of Crystallography (IUCr) (2009-2011);

-Member of the Board of the "Società dei Naturalisti e Matematici di Modena (Italy)" (2011-2013);

-Member of the Board of "Società Italiana Luce di Sincrotrone (SILS)" (2012-2015).

### SCIENTIFIC COMMITTEES

-Member of the Scientific Committee of the beamline GILDA, European Synchrotron Radiation Facility (ESRF), Grenoble, France (2000-2003);

-Member of the Scientific Committee of European Powder Diffraction Conference (EPDIC) (2005-2007);

-Member of the Scientific Committee European Crystallographic Association (ECA)-SIG (2005-2007);

-Member of the Scientific Committee of the CERIC-ERIC ELETTRA Synchrotron Facility, Trieste (Italy)(2015-to date).

### SCIENTIFIC JOURNALS

-Associate Editor of the "Periodico di Mineralogia" (2000-2006);

-Associate Editor of the "American Mineralogist" (2001-2005);

-President of the Scientific Board of "Ceramurgia+Ceramica Acta" (2002-2004).

### FULBRIGHT PARTECIPANT AND FELLOW

United States Fulbright Scholar Program participant at contest nr. 5 Academic Year 1995-96 Fulbright program.

### COVER OF THE APRIL 2015 ISSUE OF ACTA CRYSTALLOGRAPHICA B

Cover illustration of the April 2015 issue of Acta Crystallographica B (Plot of the calculated monoclinic structure model of BaTiSi<sub>2</sub>O<sub>7</sub> in the ab plane. See Fig. 8 of Viani et al. [(2015), Acta Cryst. B71, 153-163]).

### INVITED LECTURE AT THE "MONTICELLO CONFERENCE" IN THE UNITED STATES AS REPRESENTATIVE OF ITALY

On October 2017 was the only participant from Italy as Invited Lecture at the prestigious "The Monticello Conference on elongated mineral particles". Charlottesville, Virginia (USA), October 17-21, 2017.

## 2. Principal scientific publications of PI

1. Alessandro F. Gualtieri, Nicola Bursi Gandolfi, Simone Pollastri, Manfred Burghammer, Eva Tibaldi, Fiorella Belpoggi, Kilian Pollok, Falko Langenhorst, Ruggero Vigliaturo, Goran Dražić (2017). New insights into the toxicity of mineral fibres: A combined in situ synchrotron  $\mu$ -XRD and HR-TEM study of chrysotile, crocidolite, and erionite fibres found in the tissues of Sprague-Dawley rats. TOXICOLOGY LETTERS, vol. 274, p. 20-30, ISSN: 0378-4274 - **Articolo in rivista**
2. Gualtieri A. F. (2017). Sharing different perspectives to understand asbestos-induced carcinogenesis: A comment to Jiang et al. (2016). CANCER SCIENCE, vol. 108, p. 156-157, ISSN: 1349-7006 - **Articolo in rivista**

3. Andrea Bloise, Manuela Catalano, Eugenio Barrese, Alessandro Francesco Gualtieri, Nicola Bursi Gandolfi, Silvana Capella, Elena Belluso (2016). TG/DSC study of the thermal behaviour of hazardous mineral fibres. JOURNAL OF THERMAL ANALYSIS AND CALORIMETRY, vol. 123, p. 2225-2239, ISSN: 1388-6150 - **Articolo in rivista**
4. Bloise A., Barca D., Gualtieri A. F., Pollastri S., Belluso E. (2016). Trace elements in hazardous mineral fibres. ENVIRONMENTAL POLLUTION, vol. 216, p. 314-323, ISSN: 0269-7491 - **Articolo in rivista**
5. Bursi gandolfi N., Gualtieri A. F., Pollastri S., Tibaldi E., Belpoggi F. (2016). Assessment of asbestos body formation by high resolution FEG-SEM after exposure of Sprague-Dawley rats to chrysotile, crocidolite, or erionite. JOURNAL OF HAZARDOUS MATERIALS, vol. 306, p. 95-104, ISSN: 0304-3894 - **Articolo in rivista**
6. Gualtieri A. F., Nicola Bursi Gandolfi, Simone Pollastri, Kilian Pollok, Falko Langenhorst (2016). Where is iron in erionite? A multidisciplinary study on fibrous erionite-Na from Jersey (Nevada, USA). SCIENTIFIC REPORTS, vol. 6, p. 37981, ISSN: 2045-2322 - **Articolo in rivista**
7. Michele Carbone, Shreya Kanodia, Ann Chao, Aubrey Miller, Anil Wali, David Weissman, Alex Adjei, Francine Baumann, Paolo Boffetta, MD, Brenda Buck, Marc de Perrot, A. Umran Dogan, Steve Gavett, Alessandro Gualtieri, Hassan, Mary Hesdorffer, Fred R. Hirsch, David Larson, Weimin Mao... (2016). Consensus Report of the 2015 Weinman International Conference on Mesothelioma. JOURNAL OF THORACIC ONCOLOGY, vol. 11, p. 1246-1262, ISSN: 1556-0864 - **Articolo in rivista**
8. Simone Pollastri, Alessandro F. Gualtieri, Ruggero Vigliaturo, Konstantin Ignatyev, Elisabetta Strafella, Armanda Pugnali, Alessandro Croce (2016). Stability of mineral fibres in contact with human cell cultures. An in situ  $\mu$ XANES,  $\mu$ XRD and XRF iron mapping study. CHEMOSPHERE, vol. 164, p. 547-557, ISSN: 0045-6535 - **Articolo in rivista**
9. Simone Pollastri, Francesco D'Acapito, Angela Trapananti, Ivan Colantoni, Giovanni B. Andreozzi, Alessandro F. Gualtieri (2015). The chemical environment of iron in mineral fibres. A combined X-ray absorption and Mössbauer spectroscopic study. JOURNAL OF HAZARDOUS MATERIALS, vol. 298, p. 282-293, ISSN: 0304-3894 - **Articolo in rivista**
10. GUALTIERI Alessandro, POLLASTRI SIMONE, RONCHETTI Francesco, Gandolfi N. B., Albonico C., Cavallo A., Zanetti G., Marini P., Sala O. (2014). Determination of the concentration of asbestos minerals in highly contaminated mine tailings: An example from abandoned mine waste of Cretaz and Emarese (Valle d'Aosta, Italy). AMERICAN MINERALOGIST, vol. 99, p. 1233-1247, ISSN: 0003-004X, doi: 10.2138/am.2014.4708 - **Articolo in rivista**
11. POLLASTRI SIMONE, GUALTIERI Alessandro, GUALTIERI Eva Magdalena, HANUSKOVA' Miriam, Cavallo Alessandro, Gaudino Giovanni (2014). The zeta potential of mineral fibres. JOURNAL OF HAZARDOUS MATERIALS, vol. 276, p. 469-79-479, ISSN: 0304-3894, doi: 10.1016/j.jhazmat.2014.05.060 - **Articolo in rivista**
12. Viani A., GUALTIERI Alessandro, Secco M., Peruzzo L., Artioli G., Cruciani G. (2013). Crystal chemistry of cement-asbestos. AMERICAN MINERALOGIST, vol. 98, p. 1095-1105, ISSN: 0003-004X, doi: 10.2138/am.2013.4347 - **Articolo in rivista**
13. Viani, Alberto, GUALTIERI, Alessandro, POLLASTRI, SIMONE, Rinaudo, Caterina, Croce, Alessandro, URSO, Giancarlo (2013). Crystal chemistry of the high temperature product of transformation of cement-asbestos. JOURNAL OF HAZARDOUS MATERIALS, vol. 248-249, p. 69-80-80, ISSN: 0304-3894, doi: 10.1016/j.jhazmat.2012.12.030 - **Articolo in rivista**
14. Alessandro F. Gualtieri, Alberto Viani, Giulia Sgarbi, Gigliola Lusvardi (2012). In vitro biodurability of the product of thermal transformation of cement-asbestos. JOURNAL OF HAZARDOUS MATERIALS, vol. 205-206, p. 63-71, ISSN: 0304-3894, doi: 10.1016/j.jhazmat.2011.12.005 - **Articolo in rivista**
15. GUALTIERI Alessandro, Giacobbe C., Viti C. (2012). The dehydroxylation of serpentine group minerals. AMERICAN MINERALOGIST, vol. 97, p. 666-680, ISSN: 0003-004X, doi: 10.2138/am.2012.3952 - **Articolo in rivista**
16. GUALTIERI Alessandro, Veratti Linda, Tucci Antonella, Esposito Leonardo (2012). Recycling of the product of thermal inertization of cement-asbestos in geopolymers. CONSTRUCTION AND BUILDING MATERIALS, vol. 31, p. 47-51, ISSN: 0950-0618, doi: 10.1016/j.conbuildmat.2011.12.087 - **Articolo in rivista**
17. A. F. Gualtieri, B. T. Mossman, V. L. Roggli (2017). Towards a general model to predict the toxicity and pathogenicity of mineral fibres.. In: Mineral fibres: crystal chemistry, chemical-physical properties, biological interaction and toxicity.. p. 501-532 - **Contributo in volume (Capitolo o Saggio)**
18. Gualtieri, Alessandro F. (2017). Introduction [Mineral fibres]. In: (a cura di): Gualtieri Alessandro F., Mineral fibres: crystal chemistry, chemical-physical properties, biological interaction and toxicity: university textbook. EMU NOTES IN MINERALOGY, p. 1-16, LONDON:European Mineralogical Union, ISBN: 9780903056656, ISSN: 1417-2917 - **Contributo in volume (Capitolo o Saggio)**
19. GUALTIERI, Alessandro (2013). Recycling asbestos containing material (ACM) from construction and demolition waste (CDW). In: F. Pacheco-Torgal V.W.Y. Tam J.A. Labrincha Y. Ding J. de Brito. Handbook of Recycled Concrete and Demolition Waste. p. 500-525, Cambridge (UK):Woodhead Publishing,

ISBN: 0857096907 - **Contributo in volume (Capitolo o Saggio)**

20. GUALTIERI Alessandro (2012). Mineral fibrebased building materials and their health hazards. In: Fernando Pacheco-Torgal Said Jalali Aleksandra Fucic. Toxicity of building materials. p. 166-195, Cambridge (UK):Woodhead Publishing, ISBN: 0857096354 - **Contributo in volume (Capitolo o Saggio)**

### **3. Hindex of PI (only for the scientific fields in which the use of the H-index is usually adopted)**

<b>H-Index</b>	<b>Source</b>
33	Scopus

### **4. Associated investigators' Curriculum Vitae**

#### **1. RANERI Simona**

##### PERSONAL INFORMATION

Nationality: Italian

Date of birth: 08/10/1987

##### CURRENT POSITION

30/11/16 - present: Young researcher (GEO/09) (RTD-a, L.240/2010) at the Department of Earth Sciences of the University of Pisa

##### PREVIOUS POSITION

2016: Post-doctoral fellowship at the University of Catania.

##### INTERNATIONAL PROJECTS

2017-2018: EU Project Horizon 2020 Nano-cathedral (<http://www.nanocathedral.eu/>).

##### EDUCATION

2016: Ph.D. cum laude in Earth Science. Doctoral examination: 28 January 2016.

2012: Post-graduate course "Scuola di Alti Studi in Economia del Turismo Culturale", Fondazione Edoardo Garrone.

2012: M.A. in Earth Sciences, University of Catania (Italy). 110/110 cum laude.

2009: B.A. Applied Technologies for Cultural Heritages (Conservator Scientist), University of Catania (Italy). 110/110 cum laude.

##### LANGUAGE

- Italian: Native

- English: Fluent (First Certificate in English. Cambridge University. 2006)

##### MEMBERSHIP

SIMP (Italian Association of Mineralogy and Petrology), since 2014

SISN (Italian Association of Neutron Spectroscopy), since 2014

GABEC group (National research group Geo-resources, Environment and Cultural Heritage), since 2016

INTERPORE (International Society for Porous Media), since 2017

##### RESEARCH TOPICS & EXPERTISE

Non destructive and non invasive methods for geo-resources and applications: Raman spectroscopy, X-ray portable fluorescence, X-ray and neutron imaging, Nuclear Magnetic Resonance, Small Angle Neutron Scattering, 3D surface digital microscope.

##### PRINCIPAL INVESTIGATOR IN EXPERIMENTAL RESEARCHES AT INTERNATIONAL FACILITIES

2018: PI for the experimental session at Elettra (Trieste, Italy) at the TwinMic beamline (X-ray microscope). N. Experiment: 20175496. Dates: 5-11 March 2018

2018: PI for the experimental session at LLB, Saclay, France at the IMAGINE beamline (neutron imaging). N. Experiment: 347. Dates: scheduled 18-23 June 2018

#### PARTECIPATION TO EXPERIMENTAL RESEARCHES AT INTERNATIONAL FACILITIES

2016: Experimental session at LLB, Saclay, France at the PAXI beamline (small angle neutron scattering). N. experiment 12441

2014: Research stay at the Facility UGCT, Gent University (Belgium) - X-ray microtomography applications. 6th -17th May 2014.

2014: Experimental session at ILL Grenoble, France at the D11 beamline (Small Angle Neutron Scattering). doi:10.5291/ILL-DATA.9-10-1366

#### OTHER RESEARCHES ABROAD

2015: Experimental session at LLB, Saclay, France at the IMAGE beamline (neutron radiography and tomography). N. experiment 12115

2012: Experimental session at LLB, Saclay, France at the IMAGE beamline (neutron radiography and tomography).

#### SCOLARSHIPS

2017: Short Course: Micro Computed Tomography, at the 9th International Conference on Porous Media & Annual Meeting held in Delft (Netherlands) on May 12 2017.

2014: GD-SISN School - Neutron applications in Physic, Chemistry, Biology and Geology. San Giovanni in Valle Aurina (Bz, Italy) and ILL Grenoble (Francia), 13-22/09/2014.

2014: GABEC&GNM International School 2014 – Innovative methodologies for the characterization, diagnosis and conservation of the Cultural Heritages, Catania-Siracusa, 1-4/07/2014.

#### INTERNSHIP ACTIVITIES

2015: Internship activity at the NMR Laboratory of IMC – CNR Rome (Italy). Research topic: use of NMR devices. 16-21 March 2015.

2013: Internship activity at the University of Parma (Italy) – Dept of Physic and Earth Sciences. Research topic: Micro-Raman applications on minerals. 3-14 June 2013.

2013: Internship activity at the University of Parma (Italy) – Dept of Chemistry. Nanotechnologies for Cultural Heritages. Research topic: Nanomaterials and nanotechnologies. 3-14 June 2013.

2010: Internship activity at the University of Calabria, ICP-MS Laboratory. Research topic: Trace element determination of rock samples by using ICP-MS and study of obsidian by using LA-ICP-MS.

#### TEACHING EXPERIENCES

2017-2018: Lecturer of Applied Mineralogy at the MS in Earth Sciences and Technologies at the University of Pisa (Italy).

2013-2015: Teaching activity and research seminars to Master's degree students in earth Sciences at the University of Catania – Department of Biological, Geological and Environmental Sciences in the framework of Ph.D. course.

2013-present: Co-supervisor in several M.A. and B.A. thesis works.

2012: Research seminar: A multi-methodological approach for the determination of the porous structure of building stones. Fractal geometries in complex pore systems. GaBeC 2012. Rome (Italy), 21st of September, 2012.

2010/2011: Tutor for the course in Applied petrography – Bachelor's Studies in Applied Technologies for Cultural Heritages, University of Catania, Siracusa (Italy).

#### NATIONAL AND INTERNATIONAL GRANTS

2016: National Prize bestowed by the Italian Society of Mineralogy and Petrology (SIMP) for the best Doctoral thesis in material science disciplines.

2015: Research grant bestowed by Regione Siciliana in the framework of the program Misura 3: Programma SICILIA FUTURO - ORGANISMO INTERMEDIO DELLA SOVVENZIONE GLOBALE DEL PO FSE SICILIA 2007.

2015: National Prize "Angelo Bianchi" bestowed by the Italian Society of Mineralogy and Petrology (SIMP) in honor of the scientific contribute to the Italian Mineralogical and Petrological Sciences.

2014: Grant for the attendance of S.G.I. & S.I.M.P 2014 Conference, Milan, Italy.

2013: Research grant "Sportello Giovani" bestowed by AIAR for the development of a research project abroad.

2013: Grant for the attendance of the 6th International Conference on Fractals and Dynamic Systems in Geosciences, Perugia, Italy.

2011: 1st International Award - University Festival of Art, Science and Technology, Siracusa, Italy.

## NATIONAL AND INTERNATIONAL ACKNOWLEDGMENTS

2018: Convener for the scientific session Geosciences for Cultural Heritages at the Congresso congiunto SGI-SIMP 2018, Catania, 12 – 14/09/2018  
2018: Invited professor. ERASMUS+ STAFF MOBILITY FOR TEACHING PROGRAM, inter-institutional agreement 2017-2020, University of Pisa, Dept. Earth Sciences and University of Montaigne-Bordeaux, IRAMAT Lab. (France).  
2018: Member of the Organizing Committee for the XIII GeoRaman International Conferences, Catania, 10-14 June 2018.  
2017: Member of the Organizing Committee for the national conference "Conservazione e restauro del materiale lapideo in Piazza dei Miracoli: l'esperienza del progetto Nanocathedral (EU Project 646178)", Arte (è) Scienza, Pisa, 1 Dicembre 2017  
2017: Invited professor. ERASMUS+ STAFF MOBILITY FOR TEACHING PROGRAM, inter-institutional agreement 2017-2020 University of Pisa, Dept. Earth Sciences and University of Gent Dept. of Chemistry (Belgium). Dates: 28-29 September 2017.  
2017: Invited speaker at the 6th Technical Meeting Nano-Cathedral Project (Grant Agreement No 646178), Vienna (Austria), 22-24 November 2017.  
2017: Invited speaker - key note lecture at the SIMP-SGI-SOGEI-AVI Conference with the contribute "Effectiveness, compatibility and durability of consolidants for marble: a review of the last ten year of researches", Pisa, 05.09.2017.  
2017: Invited speaker at the 5th Technical Meeting Nano-Cathedral Project (Grant Agreement No 646178), Olso (Northway), 7-8 June 2017.  
2017: Public workshop: The Nano-Cathedral Project (Grant Agreement No 646178) at the University of Catania, Dept of Biological, Geological and Environmental Sciences. 06.04.2017  
2016: Organizer support for the 2nd European Mineralogical Conference EMC 2016 (Rimini, Italy 11 - 15 September 2016). Minerals, rocks and fluids: alphabet and words of planet Earth  
2016: Invited speaker at the Dept. of Chemistry of the Univ. of Parma for seminars, 26.10.2016.  
2016: Invited speaker at the Dept. of Chemistry of the Univ. of Parma for seminars, 26.05.2016  
2015: Member of the Organizing and Scientific Committee for the National Conference "Diamonds and Colored Gems" since 2016.  
- Member of the Editorial Board of Journal of Powder Metallurgy & Mining and Journal Archaeology and Antropology  
- Reviewer for Mediterranean Archaeology and Archaeometry, Studies in Conservation, Journal Raman Spectroscopy, Journal of Archaeological Science, Journal of Cultural Heritage, Periodico di Mineralogia, Bulletin of Engineering Geology and the Environment

## 2. BALLIRANO Paolo

### PERSONAL INFORMATION

Nationality: Italian

Date of birth: 02/11/1964

### CURRENT POSITION

02/11/2016: Full Professor at the Department of Earth Science of Sapienza University of Roma.

### PREVIOUS POSITION

01/01/2005-01/11/2016: Associate Professor at the Department of Earth Science of Sapienza University of Roma.

01/03/1999-31/12/2004: Researcher at the Department of Earth Science of Sapienza University of Roma.

01/10/1998-31/02/1999: In charge of the X-ray diffraction laboratories of CTG SpA Italcementi group, Bergamo.

01/11/1994-31/10/1996: Post Doc position at the Department of Earth Sciences of the University of Pisa.

01/09/1991-01-05/1992: Visiting Scientist at the Departments of Geology and Chemistry/Biochemistry, Arizona State University, Tempe, USA

### EDUCATION

1994: Ph.D. in Earth Sciences at the Department of Earth Science of Sapienza University of Roma.

1990: M.A. cum laude in Geological Sciences at the Department of Earth Science of Sapienza University of Roma.

### LANGUAGE

- Italian: Native

- English: Fluent

### MEMBERSHIP

GMR (Gruppo Mineralogico Romano) since 2007 Honorary member.

SIMP (Società Italiana di Mineralogia e Petrologia) since 1994.

Active Member of ICDD (International Center for Diffraction Data) since 1997

AIC (Associazione Italiana di Cristallografia) 1994-2006

MSA (Microscopy Society of America) 1992-1995

MSA (Mineralogical Society of America) 1992-2003

MAC (Mineralogical Association of Canada) 1992-1999

#### RESEARCH TOPICS & EXPERTISE

- crystal chemical and structural characterization by modern analytical methods (X-ray powder and single-crystal diffraction, Transmission and Scanning Electron Microscopy, X-ray absorption, IR, Raman and Mössbauer spectroscopy etc.), even at non-ambient condition, of zeolites and pseudo-zeolites, fibrous minerals, carbonates, sulphates, nitrates, oxides and nano-oxides, pigments, cement materials, ionic liquids and inorganic and organic compounds.

- development of new X-ray instrumentations and their application to structural analysis and the kinetics of phase transitions.

- crystal chemical and structural characterization of both pristine and differently treated (Fe-doped, Simulated Lung Fluids SLFs-leached) samples of regulated and non-regulated mineral fibres, erionite in particular, by specifically optimizing micro-analytical techniques.

Acts as referee for several journals in the fields, besides mineralogy, of crystallography, materials science, crystal growth, physical-chemistry, organic and inorganic chemistry.

Author or co-author of more than 230 papers, book chapters, and congress communications, mainly at international level.

#### TEACHING EXPERIENCES

2001-present: Supervision of several Bachelor and Master Theses as well as PhD projects.

2000-present (Sapienza University of Roma): "Cristallografia", "Tirocinio su Minerali e Rocce", "Minerochimica e Tecnologia dei Cementi", "Mineralogia e Laboratorio I (M-Z)", "Metodologie Diffrattometriche Avanzate", "Mineralogia e Laboratorio (M-Z) DM 509/99", "Minerofisica", "Mineralogia Modulo I DM 270/04", "Mineralogia (M-Z) DM270/04", "Museologia e Divulgazione Mineralogica"

1996-1997 (Sapienza University of Roma) as Teaching Assistant: "Mineralogia Sistemática", "Mineralogia" and "Laboratorio di Mineralogia"

1993-1996 (University of Chieti "G. D'Annunzio") as Teaching Assistant: "Mineralogia" and "Laboratorio di Mineralogia".

#### NATIONAL AND INTERNATIONAL GRANTS

2015: Un sistema multifunzionale SAXS/GISAXS/WAXS (small/grazing incidence/wide angle X-ray scattering) per la caratterizzazione strutturale di sistemi solidi e in soluzione su scala meso e nanoscopica: Co-PI (Co-Principal Investigator). Acquisizione di Grandi Attrezzature Scientifiche Sapienza. 590.000 €

2014: Crystal chemical and structural modifications of erionite fibres leached with simulated lung fluids. PI. Progetti di Ricerca Sapienza. 5.000 €

2010: Protic Ionic Liquids: a structural and spectroscopic study by means of experimental and computational techniques: I. Progetti di Ricerca Sapienza. 85.000 €

2009: Studio strutturale su solfati di calcio idrati mediante dinamica molecolare e diffrazione RX su polveri e cinetiche di trasformazione di fase nel sistema CaSO<sub>4</sub>-H<sub>2</sub>O: PI. Ateneo federato di Scienza e della Tecnologia (AST) Progetti assegnati di ricerca Sapienza. 18.976,84 €

2007: Third party takings (including acquired goods). X-ray powder diffraction laboratories and Rectorial Laboratory Fibres and Inorganic Particulate. > 100.000 €

2006: Stabilità termica, progetti di ordine/disordine e cinetiche di trasformazione di fase in minerali ed equivalenti di sintesi mediante diffrattometria RX su polveri: PI. Ateneo ex 60% Sapienza. 31.600 €

2004: Cristallografia e cinetica delle trasformazioni di fase in funzione della temperatura: PI. Acquisizione e manutenzione di medie e grandi attrezzature Sapienza. 120.000 €

2003: Diffrattometria su polveri: applicazioni avanzate mediante il metodo Rietveld: PI. Ateneo ex 60% Sapienza. 3.800 €

Since 2003 he has been funded for a total of ca. 1M€ by Sapienza University of Roma for several research projects he has managed as Principal or Co-Principal Investigator. Moreover, he has been member of different research projects funded by MIUR in both GEO and CHIM SSDs.

2003: NATO Travel Grant for attending the International School of Crystallography "High Pressure Crystallography", held in Erice, Italy. 1997 European Mineralogical Union (EMU) Travel Grant for attending the "Modul'97" International school, held in Budapest, Hungary.

1992: NATO Travel Grant for attending the International School of Crystallography "Modern Perspective in Inorganic Crystal Chemistry", held in Erice, Italy.

#### NATIONAL AND INTERNATIONAL ACKNOWLEDGMENTS

2017: Member of the Scientific Committee and invited speaker at the EM? International School entitled "Mineral fibres: crystal chemistry, chemical-physical properties, biological interaction and toxicity" held in Modena, June 19-23, 2017.

2016-present: Named as Member of the Technical Group on "the analysis of asbestos in soils aimed at the management of lands and rocks from excavations", Italian Ministry of Health.



2016-present: Chair of the Department of Earth Sciences of Sapienza University of Roma.

2016: Chief Editor and Section Editor (Mineralogy) of the international journal Periodico di Mineralogia.

2014-present: Member of the Steering Committee of the Centre for Nanotechnology Applied to Engineering (CNIS) of Sapienza University of Roma.

2012-2013: Research Committee of Sapienza University of Roma being in charge of selecting for funding, for a total of ca. 10M€/year, the yearly submitted research projects.

2012: Chairman of the session entitled "Characterization Techniques for Functional Properties" at Nanoforum 2012, held in Roma on September 24-26, 2012.

2010-present: Scientific Coordinator of the Rectorial Laboratory Fibres and Inorganic Particulate of Sapienza University of Roma; this laboratory, which has been established with DR n. 1122 October 4, 2001, has been authorised by the Centre for the Control of Illnesses of the Italian Ministry of Health ("CCM: Centro Controllo Malattie") DGPREV 0015147, June 23, 2011, to perform certified analyses by MOCF (Phase Contrast Optical Microscopy), SEM-EDX, FTIR e DRX, aimed at identifying and quantifying asbestos on both raw materials and airborne particulates.

2010-present: Named as Member of the Commission on Safety of Sapienza University of Roma.

2010-2014: Named as Member of the Commission on Scientific Conferences of the Faculty of Mathematical, Physical and Natural Sciences, Sapienza University of Roma.

2010-2014: Named as Member of the Commission on Cultural Initiatives of the Faculty of Mathematical, Physical and Natural Sciences, Sapienza University of Roma.

2009-2010: Elected as Representative of the Associate Professors in the Academic Counsel of Ateneo federato di Scienza e della Tecnologia (A.S.T.), Sapienza University of Roma.

2008: The mineral Balliranoite (Chukanov et al., 2010: Eur. J. Mineral. 22, 113-119) has been named as recognition of his work on cancrinite-group minerals.

2008: Member of both the Organizing and Scientific Committee, and acted as Invited Speaker, of the International Mineralogical School, organized by GNM, entitled "HP-HT - Mineral Physics Implications for Geosciences", held in Bressanone on February 11-15, 2008.

2007: Member of the Directorial Board of the National Group of Mineralogy (GNM) for 2007-2009.

2007: Member of the Organizing Committee of the Workshop sponsored by GNM and entitled "Minerals and Health", held in Rome on June 14-15, 2007.

2003: Included, according to the Italian Ministry of Instruction and University (MIUR) decree n. 1543 September 8, 2003, in the Italian List of Experts ("Albo degli Esperti").

2003: Member of the Scientific Committee, and lecturer, of the "Experimental Schools of Energy Dispersive (EDXD) and Angular Dispersive (ADXD) X-ray Diffraction", held in Rome: September 8-20, 2003.

2002: Member of the Scientific Committee, and lecturer, of the "Experimental Schools of Energy Dispersive (EDXD) and Angular Dispersive (ADXD) X-ray Diffraction", held in Rome: September 9-21, 2002.

2001: Member of the Scientific Committee, and lecturer, of the "Experimental Schools of Energy Dispersive (EDXD) and Angular Dispersive (ADXD) X-ray Diffraction", held in Rome: September 10-22, 2001.

2000: Member of the Scientific Committee, and lecturer, of the "Experimental Schools of Energy Dispersive (EDXD) and Angular Dispersive (ADXD) X-ray Diffraction", held in Rome: September 4-16, 2000.

1999: Member of the Scientific Committee, and lecturer, of the "Experimental Schools of Energy Dispersive (EDXD) and Angular Dispersive (ADXD) X-ray Diffraction", held in Rome: June 14-26, 1999.

1998: Awarded by SIMP of the "Ugo Panichi Prize" as the best Italian young researcher in the mineralogical field for 1996-1998.

1994: Awarded with the SIMP (Società Italiana di Mineralogia e Petrologia) prize for the best Ph.D. thesis of the year of mineralogical subject.

### **3. OTTAVIANI Maria Francesca**

Maria Francesca Ottaviani

Full Professor in Physical Chemistry at the University of Urbino "Carlo Bo"

#### CURRICULUM VITAE

#### PERSONAL INFORMATION

Name: MARIA FRANCESCA OTTAVIANI

Address: VIA CAPO DI MONDO, 25, 50136 FIRENZE, ITALY

Telephon: +39-3487354856

Fax: +39 0722 304222

E-mail: maria.ottaviani@uniurb.it

Nationality: Italian  
Birthday: 16 JANUARY 1951

#### ACADEMIC CURRICULUM

- Date (from – to): 1981-1998
- Job position: Assistant Professor
- location: Department of Chemistry, University of Florence-Italy
  
- Date (from – to): 1998-01/2017
- Job position: Associate Professor in Physical Chemistry - Teaching Physical Chemistry in the Laurea Courses: Environmental Sciences, Biological Sciences, Cultural Heritage, Pharmaceutical Chemistry and Technology (CTF)- Teaching “Energy Sources” at LM75
- location: Department of Chemistry at the University of Florence – Department DiGEOTECA - DiSTEVA - DiSPeA University of Urbino
  
- Date (from – to): 2004-2009
- Job position: National Qualification to Full Professor
  
- Date (from – to): 2014-01/2017
- Job position: National Qualification to Full Professor position
  
- Date (from – to): 02/2017-today
- Job position: Full Professor in Physical Chemistry – Teaching Physical Chemistry in the Laurea Courses of Biological Sciences and CTF
- location: DisPEA at the University of Urbino

#### EDUCATION, TRAINING AND QUALIFICATIONS AT ITALIAN AND FOREIGN UNIVERSITIES

- Date (from – to): 1969-1974
- Education: Master Degree in Chemistry with Full Marks and Lude - PhD
  
- Date (from – to): 1974-1981
- Qualification: University fellowship
  
- Date (from – to): 1991
- Qualification: Post-Doc at the University of Wageningen, the Netherlands
  
- Date (from – to): 1992-1994
- Qualification: Post-Doc at Columbia University, New York, USA
  
- Date (from – to): 1994-1996
- Qualification: Senior Associate Scientist at Columbia University, New York, USA
  
- Date (from – to): 1996-2013
- Qualification: Invited Professor at Columbia University, New York, USA
  
- Date (from – to): 2014-today
- Qualification: Invited Professor at The Hebrew University of Jerusalem, Israel
  
- Date (from – to): 2011-2012 e 2016-today

- Qualification: Invited Professor (External Scientific Fellow) at the University of Lodz, Poland

PUBLICATIONS: n. publications in international scientific Journals at high impact factor: 218

H-INDEX (Scopus): 35

#### SCIENTIFIC AND RESEARCH SKILLS AND COMPETENCES

Main Research Subjects:

- (a) Characterization by means of electronic magnetic resonance techniques of carriers of active ingredients, drugs, dendrimeric drugs and other drugs and their interactions with biomolecules and biostructures
- (b) Characterization of non-porous and nano-porous solids for biocatalysis and superficial toxicity
- (c) Characterization of organic photovoltaic dye-sensitized solar cells (DSSC)
- (d) Characterization of oil-based food and cosmetic matrices

#### DIDACTICS

ACTUAL TEACHING COURSES AT THE UNIVERSITY OF URBINO: Physical Chemistry, for CTF – Biological Physical Chemistry, for Biological Sciences – Physical Chemistry for Cultural Heritage, for Conservation and Restoration of Cultural Heritage

FURTHER PREVIOUS TEACHING COURSES AT THE UNIVERSITY OF URBINO: Energy Sources, Environmental Physical Chemistry, Metodologies for environmental analysis.

#### CONFERENCES: LECTURES AND ORGANIZATION - TEACHING AT SPECIALIZING AND FINE-TUNING SCHOOLS:

- More than 150 invited lectures at national and international Congresses
- 65 invited lectures in Universities and Industries.
- Organization of 24 national and international Congresses
- Teaching at specializing courses in "restoration of polluted sites", "applied cytometry", "electron magnetic resonance", "physical-chemical techniques for biological, pharmacological and environmental analyses", "food chemistry"

#### ORGANIZATION SKILLS, MEMBER OF COMMITTEES AND RESPONSABILITY ROLES AT ACADEMIC LEVEL:

- (A) LEADER OF THE PHYSICAL CHEMISTRY GROUP – UNIVERSITY OF URBINO
- (B) LEADER OF THE LAB. IN ELECTRON MAGNETIC RESONANCE – UNIVERSITY OF URBINO.
- (C) PRESIDENT OF THE LAUREA AND MASTER COURSE IN ENVIRONMENTAL SCIENCES (2008-2010)
- (D) MEMBER OF THE MANAGEMENT COMMITTEE - LEADER OF THE WORKING GROUPS ON MATERIALS CHARACTERIZATION IN THE COST ACTIONS TD0802 AND MP1202 (2010-2017)
- (E) MEMBER OF THE MANAGEMENT COMMITTEE OF THE ITALIAN GROUP OF ELECTRON MAGNETIC RESONANCE ,GIRSE (2012-2014)
- (F) MEMBER OF THE COMMITTEES FOR THE BUDGET DISTRIBUTION AT THE DEPARTMENTS DISTEVA AND DISPEA- UNIVERISTY OF URBINO.
- (G)MEMBER OF THE FOLLOWING COMMITTEES AT THE UNIVERSITY OF URBINO: PARITETIC COMMITTEE STUDENTS-PROFESSORS FOR PHARMACY AND CTF; COMMITTEE FOR THE REVISION OF THE ORGANIZATION OF BIOLOGY LAUREA COURSE; COMMITTEE FOR THE TRAINEESHIPS FOR THE BIOLOGY LAUREA

COURSE, COMMITTEE OF THE STATE EXAMINATION FOR THE PROFESSION OF BIOLOGIST  
(F) MEMBER OF COMMITTEES FOR PHD CONCOURSES AND FINAL DEFENCES IN ITALIAN UNIVERSITIES (FLORENCE, PADUA, NAPLES, TURIN, URBINO) AND FOREIGN UNIVERSITIES (COLUMBIA UNIVERSITY – NY-USA, UNIVERSITY OF MADRID AND ALCALA'-SPAIN)  
(H) RESPONSABILITY AND ORGANIZATION OF THE LAUREA HONORIS CAUSA FOR PROF. CARLO RUBBIA – UNIVERSITY OF URBINO- 27/03/2013  
(I) RESPONSABILITY AND ORGANIZATION OF THE INVITED LECTURE OF PROF. LUIGI DEI – RECTOR OF THE UNIVRSITY OF FLORENCE, ITALY – 5/5/2016

INTERNATIONAL COLLABORATIONS:

COLUMBIA UNIVERSITY- DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, NY,USA  
MASSACHUSETTS INSTITUTE OF TECHNOLOGY (MIT), USA  
HEBREW UNIVERSITY OF JERUSALEM – CASALI INSTITUTE OF APPLIED CHEMISTRY, ISRAEL  
UNIVERSITY OF MIAMI, FLORIDA, USA  
CNRS OF MONTPELLIER, FRANCE  
CNRS OF MARSEILLES, FRANCE  
CNRS OF TOULOUSE, FRANCE  
UNIVERSITY OF ALCALA, MADRID, SPAIN  
UNIVERSITY OF DRESDEN, GERMANY  
UNIVERSITY OF LODZ, POLAND  
UNIVERSITY OF YORK, UK  
UNIVERSITY OF ATHENS, GREECE  
UNIVERSITY OF COPENHAGEN, DENMARK  
UNIVERSITY OF SOFIA, BULGARIA  
NATIONAL R&D INSTITUTE FOR NON-FERROUS AND RARE METALS, PANTELIMON, ILFOV, ROMANIA  
SUPSI, ICIMSI, MANNO, SWITZERLAND  
KAOHSIUNG MEDICAL UNIVERSITY, TAIWAN

COLLABORATIONS, AGREEMENTS, AND CONTRACTS WITH INDUSTRIES AND FINANCING INSTITUTIONS:

NATIONAL SCIENCE FUNDATION (NSF) (2000-2008)  
NATO (1992 - 2001)  
GRANTS OF THE ITALIAN MINISTRY OF THE PUBLIC EDUCATION (EX 60 %) (1993-2004)  
PRIN (EX 40 %) (2000-2016) .  
JOINT EUROPEAN MEDICAL RESEARCH BOARD (JEMRB) (1997-1999)  
MONTEDISON-MONTEFLUOS, (1983-1991)  
UNILEVER S.P.A. , NEW YORK CORPORATION, USA (2002-2017)  
MOLTENI S.P.A, FLORENCE, ITALY (2002-2003)  
VETROTEX S.P.A., MILAN, ITALY (2002-2006)  
BUZZI-UNICAL S.P.A., FLORENCE, ITALY (2007-2009)  
AS-TECHNOLOGY E PHOTOENERGY S.R.L, SAN MARINO. (2008-2011)  
C.I.S. S.P.A , FLORENCE, ITALY (2009-2011)  
SCARLINO ENERGIE S.R.L., FLORENCE, ITALY (2013-2017)  
TELORMEDIX S.A., BIOGGIO, SWITZERLAND (2013-2014)  
BICARJET S.R.L., PADUA, ITALY (2014-2015)  
ENERSOL S.C.R.L., RIMINI, ITALY (2014-2017)  
W.LADURNER SRL, BADIA POLESINE (RO), ITALY (2014-2017)

**4. BASSI Anna Maria**

Anna Maria Bassi

## EDUCATION:

1973: High School Degree, Liceo specializing in classical studies "C. Colombo" Genova, Italy

1978: Biologist Science Degree, 110/110 cum laude, School of Biological Sciences, University of Genova Italy

1983: Fellowship in General Pathology, 50/50 cum laude, School of Medicine, University of Genova. Italy

## CHRONOLOGY OF EMPLOYMENT AND SUPPORT

1986- : Assistant Professor of Pathology, SSD MED04, University of Genova, Italy

1986-1997: General Pathology Inst., University of Genova Italy

1997 – Department of Experimental Medicine, University of Genova Italy

1986 – 2005: Faculty of Medicine and Surgery, University of Genova Italy

2005-2012: Faculty of Mathematic, Physic and Natural Sciences, University of Genova, Italy

2012 -: School of Medical and Pharmaceutical Sciences, University of Genova, Italy

2015- Associate Researcher at Institute of Biophysics, CNR, Genoa, Italy

## Current teaching appointments

- General pathology, immunology and laboratory (Biological Sciences - Bachelor's Degree)

- Clinical pathology ( Molecular And Sanitary Biology Master's Degree)

- Physiopathology (Medicine and Surgery Master's Degree)

- General Pathology – Integrated Course (Nursing Bachelor's Degree)

Medicine Fellowship courses: Clinical pathology, Medical Genetic, Anesthesiology, Neurology, Medical Rehabilitation, Plastic Surgery, Rheumatology, Medical Toxicology, Pathological Anatomy – University of Genoa

PhD courses and II level Masters

## Organizational skills and competences

2018- : Vice-Director of CENTRO 3R- Interuniversity Center for the Promotion of the Principles of the 3Rs in Teaching and Research- Convention Universities of Pisa and Genoa, Italy.

Responsible of University of Genova Unit of Centro 3R

2008- : Person in charge for Laboratory Analysis and Research in Physiopathology (LARF, Quality assurance as ISO9001:2008, DIMES –Pathology Sect.)

2003- : Head research of: In vitro toxicology projects, LARF-DIMES

2008- : Responsible of Scientific Committee and Organization of Theoretical and Training Courses on alternative methods

- 6 Editions of Basic Course "CELL CULTURE: THE RULES OF ALTERNATIVE METHODS in accordance to EU laws " (17 ECM) - Genoa, (2 days)

- 3 Editions of Advanced Course - " TO GIVE A SENSE TO ALTERNATIVE METHODS TO ANIMAL EXPERIMENTATION" – (19 – 21 ECM) – Genoa (2 days)

- From cell to QSAR: "PREDICTIVE ALTERNATIVE MODELS IN TOXICOLOGY" (24 ECM), Genoa, 2016 (3 days)

- Oxidative stress: impact on pathophysiological processes, its determination and modulation. Genoa. 2010

- CELL CULTURE: THE RULES OF ALTERNATIVE METHODS in accordance to REACH" (16 ECM) - Genoa, 2009

- CELL CULTURE: APPLICATIONS (12 ECM) – Genoa 2008.

## Expert Commissions

2016- Member of Technical/scientific Experts of Table for Alternative Methods, Italian Health Ministry, Rome, Italy

2011- Member of National Reference Center for "Alternative Methods, Health and Care of Laboratory Animals". (11A08025) DL 20.04.2011 Italian Health Ministry, Registered by Corte dei conti 26.05.2011)

- in vitro methods - TICASS - Innovative Technologies for the Environmental Control and Sustainable Development - Managing Body Polo Regional Innovation Ligure "Energy / Environment", Genoa

- Solution provider NineSights Community (NineSigma)

- Seventh Research Framework Programme (EUROPEAN COMMISSION)

- Council member Gerson Lehrman Group Healthcare Council, USA.

## Membership of:

- Italian Society for In vitro Toxicology (CellTox )

- European Society For Alternatives To Animal Testing (EUSAAT)

- European Society Of Toxicology In Vitro (ESTIV)

- International Society for In Vitro Methods (IN VITROM)
  - Society for Free Radical Research (SFRR)
  - Società Italiana di Cancerologia (SIC)
  - European Association for Cancer Research (EACR).
  - ForumMediterraneo – Comparative oncology
  - Board Membership “ The Open Toxicology Journal”
  - CRESIS (Research Center for Ecocompatibility, Safety and Innovation of chemical compounds), University of Genova, Italy
- Invited Reviewer for several Peer-review journals (Elsevier reviewer)

#### RESEARCH ISSUES

- Assessment of 3D in vitro models, physiological relevant, by use of millifluidic bioreactors, to study human pathways diseases, to evaluate strategic preventive/therapeutical strategies.
- Evaluation of biomarkers for pathogenesis, prevention and therapy of human glaucoma on 3D dynamic cultures of human Trabecular meshwork cells
- evaluation of biological potential of chemicals, natural and synthetic, and signalling pathways to be related to cellular response to stressors.
- in vitro differentiation protocols for adult stem cells
- Analysis of molecular pathways of antitumoral effects of natural and synthetic compounds,

Coauthorship of more than 160 scientific papers, most of them on international experimental research journals (ISSN, ISSB and ISI), chapters of scientific books, and abstracts/contributions at international meetings.

#### Recent scientific awards:

- Within the five finalists for Training Prize Category of 2014 LUSH PRIZE supporting animal-free testing , London 14.11. 2014
- Winner of LUSH Prize Award 2013 supporting animal-free testing, London 13. 11.2013
- Within the four finalists for Science Prize Category of 2012 LUSH PRIZE supporting animal-free testing, London 15.11. 2012

#### Patent

- Hydrogel Scaffold for 3D cultures (Caviglioli, G.; Baldassari, S.; Zuccari, G.; Bassi A. M.; Yan, M.) approved by Spin off and Patents Commission – University of Genoa, Italy. Italian Depository Number: 8102017000087978, 29/09/2017

#### Recent public engagement and invited speakers

- Italian Spokesperson for In vitro toxicology at “3Rs & Policy Making at the European Parliament” Brussels, 27.01.2015
  - Alternative methods for a personalized medicine, based on clinical evidence, Meeting “Animal models for study human diseases”, Foundation of zooprophyllactic and zootechnical initiatives, Brescia, 20.04 2017
  - 3Rs and alternative methods to animal testing for scientific purposes. Education Course “Protection of animals used in research: regulatory, ethical and scientific aspects” University of Pisa, 22.04.2016
  - Acute and chronic Inflammation, Meeting “Come to Quantum: Interoception, inflammation and Autonomic Nervous System”, Genova 7.05.2016
  - Integrated Medicine: old and new model, lifestyles and shared therapies, Report on Aloe Effects on Immune System, results of in vitro studies. Grosseto 30.04.2016
  - Modulation of redox response in human tumor cell lines in vitro approach and in vitro evidence. CEROVEC Workshop: Oxidative stress and research: new horizons in comparative oncology Genova, 9.12. 2013.
  - LUSH PRIZE CONFERENCE “21st Century Compassion” – report on “Organization of training courses on in vitro methods in Genoa, Italy”, Londra (UK), 13.11.2013
- Interview for several newspaper and scientific news

#### Recent FUND RAISING

Research Unit Head:  
2017:

- Euro Trans-Bio Project – @IgaWarning - A comprehensive service for in situ monitoring, automatic counting and risk evaluation of toxigenic microalgae. (2018-2020)
- Research Award A.I.S.G. – Omikron Italia, "Marco Centofanti" for Neuroprotection and glaucoma: Assessment of a 3D physiological relevant model for study primary open-angle glaucoma (2018-2020)
- 2014:
  - EuroTransBio Project: Innovative high throughput high content neurotoxicity assay based on human adipose tissue-derived stem cells (Responsible of one of Operative Units of University of Genoa)
- 2013:
  - Italian Health Minister – Current Research - Responsible of Operative Unit for "Oxidative stress in tumor stem cells: biology and modulation strategies" Principal Investigator Dott.ssa Alessandra Ratto (IZT - Piemonte, Liguria e Valle d'Aosta)

#### Scientific Research responsible

2012-2014: two-year research grant - OP CRO European Social Fund Liguria Region 2007-2013 Axis IV "Human Capital" ob. specific I / 6 to 2012. Project "In vitro evaluation of the scenario of risk to human health from exposure to ash and mixtures derived from disposal of certain categories of waste: development of in vitro tests in accordance with the European guidelines"

#### Responsible for Scientific Research Contracts / Advices:

- 2017- HUWELL CHEMICALS S.P.A., MI, Italy- CEPRA s.r.l. –Casalecchio di Reno (BO): Bibliographic research and Klimish evaluation of Mercaptoethylamine Hydrochloride (CAS 156-57-0; EC 205-858-1), as required by the VII annex of Reach Regulations.
- 2016- CPG Lab Srl, Genova: "In vitro study on the potential skin irritation/corrosion of chemical compounds on reconstructed human skin models, according EU laws"
- 2011- IREOS Laboratories Srl, Genova: "In vitro study on the potential skin irritation/corrosion of chemical compounds on reconstructed human skin models, according EU laws"
- 2015: BioService s.r.l., Castelmassa (RO), Italy: Multidisciplinary approach for in vitro analysis of biological potential of two tissue Healing formulations
- 2012: Bausch & Lomb Incorporated Grants & Charitable Contribution Evaluation of oxidative stress levels in conjunctiva epithelium of dry eye patients, normal subjects and dry eye patients in therapy with hyaluronic acid 0.24% eyedrops preservatives free "
  - Aloe Association - Masio (AL), Italy, for the project "In vitro study on the potential for skin irritation two creams with/without aloe on in vitro models of normal human keratinocytes"
  - Sharper Therapeutic: Evaluation of oxidative stress biomarkers in a chemiotherapeutic regimen in association with antioxidant integrator.
- 2011: Betafarma SpA-Cesano Boscone (MI) Italy: In vitro study on the cytotoxic potential of Cement Root canal President Cefinal Endocem of a line of human keratinocytes"
- BIAD REACH Consortium - Colleterto Giacosa (TO) Italy for "Literature search on the physico-chemical, toxicological and eco-toxicological effects in vivo and in vitro (according to EU standards), for glycocholic, ursodeoxycholic, chenodeoxycholic acids. data analysis scientific report, analysis of the Data Gap and literature...

#### **5. PROCOPIO Antonio Domenico**

- (2015-) Director of the School of Specialization in Clinical Pathology and Clinical Biochemistry, Marche Polytechnic University, Ancona
- (2014-) Rectoral Delegate, UPM-INRCA Joint Committee.
- (2013-) Director, Section of Experimental and Labor Pathology, DISCLIMO Department, Marche Polytechnic University, Ancona.
- (2011) Director of the Center for Clinical Pathology and Innovative Therapy, INRCA - SCIENTIFIC INSTITUTE (IRCCS) - Ancona
- (2007-2011) Technical coordinator and member of the Cabin of Direction "Research and Innovation", Marche Region.
- (2006-) Coordinator of the PhD in Environmental and Industrial Pathologies, Marche Polytechnic University, Ancona.
- (2006-) Director of the Postgraduate School in Clinical Pathology, Marche Polytechnic University, Ancona.
- (2005-07) Member of the National Commission for Health Research, Ministry of Health, Rome.
- (2004- ) Director, Centre of Clinical Pathology and Innovative Therapies, Centre of Cytology, Laboratory of Clinical Pathology, National Institute on Aging INRCA-IRCCS, Ancona, Italy.
- (2003-2008) Director, Department of Clinical and Molecular Science, Università Politecnica delle Marche, Ancona, Italy.
- (2002-2007) Acting Professor of General Pathology, Faculty of Pharmacy, "Carlo Bo" University, Urbino, Italy.
- (2001-2002) Director, Institute of Experimental Pathology, University of Ancona, Italy.
- (2000- ) Full Professor of General and Clinical Pathology, Faculty of Medicine, Polytechnic University of Marche, Ancona, Italy.
- (2000-2001) Acting Professor of Immunology, Faculty of Medicine, University of Ancona, Italy.

- (2000-2001) Director, Clinical Pathology Laboratories (I and II), "SS Annunziata" University Clinical Hospital, Chieti, Italy.
- (1998-2000) Director, Clinical Pathology Laboratory, "S. Camillo de Lellis" Hospital, Chieti, Italy.
- (1997-2000) Acting Professor of Clinical Pathology, Faculty of Medicine, "G. D'Annunzio" University, Chieti, Italy.
- (1997-2000) Director, Clinical Pathology, Department of Oncology and Neuroscience, "G. D'Annunzio" University, Chieti, Italy.
- (1992-2000) Associate Professor of General Pathology, Faculty of Medicine, "G. D'Annunzio" University, Chieti, Italy.
- (1993) Adjunct Scientist, NICHID, NIH, Bethesda, MD.
- (1989-1990) Guest Scientist-FIRC Fellow, Biochemistry and Immunopharmacology Section, Laboratory of Immunology, NIAID, NIH, Bethesda, MD.
- (1988-1992) Assistant Professor, Department of Experimental Medicine, University of L'Aquila, Italy.
- (1986-1987) Wellcome, Italia Fellow in Immunology and Pathology at the Institute of Experimental Pathology, "La Sapienza" University, Rome, Italy.
- (1983-1985) Fogarty International Fellow, Biological Therapeutics Branch, National Cancer Institute-Frederick Cancer Research Facility, National Institutes of Health, Frederick, Maryland.
- (1980-1984) Post-graduate training and residency in Pathology, "La Sapienza" University Hospitals, Roma, Italy

## 5. Principal scientific publications of associated investigators

### 1. RANERI Simona

- Barone, Germana, Bersani, Danilo, Mazzoleni, Paolo, RANERI, SIMONA (2017). Portable XRF: a tool for the study of corundum gems. OPEN ARCHAEOLOGY, vol. 3, p. 196-203, ISSN: 2300-6560, doi: 10.1515/opar-2017-0011 - **Articolo in rivista**
- Barone, Germana, Di Bella, Marcella, Mastelloni, Maria Amalia, Quartieri, Simona, RANERI, SIMONA, Sabatino Giuseppe (2017). Pigments characterization of polychrome vases production at Lipàra: New insights by noninvasive spectroscopic methods. X-RAY SPECTROMETRY, ISSN: 0049-8246, doi: 10.1002/xrs.2810 - **Articolo in rivista**
- Lezzerini M., Raneri S., Nutarelli M., Luti L (2017). Conservation of cultural stones: relationship among texture, thermal ageing and consolidation strategies in white Apuan marbles. JOURNAL OF MINERAL, METAL AND MATERIAL ENGINEERING, vol. 3, p. 46-57, ISSN: 2414-2115 - **Articolo in rivista**
- Barone G, Bersani D., Lottici P.P., Mazzoleni P., Raneri S., Longobardo U. (2016). Red gemstone characterization by micro-Raman spectroscopy: the case of rubies and their imitations. JOURNAL OF RAMAN SPECTROSCOPY, vol. 47, p. 1534-1539, ISSN: 0377-0486, doi: 10.1002/jrs.4919 - **Articolo in rivista**
- Barone Germana, Bersani Danilo, Coccato Alessia, Lauwers Debbie, Mazzoleni Paolo, Raneri Simona, Vandenabeele Peter, Manzini Davide, Agostino Giuseppe, Neri Nicola Francesco (2016). Nondestructive Raman investigation on wall paintings at Sala Vaccarini in Catania (Sicily). APPLIED PHYSICS. A, MATERIALS SCIENCE & PROCESSING, vol. 122, 838, ISSN: 0947-8396, doi: 10.1007/s00339-016-0370-7 - **Articolo in rivista**
- Barone Germana, Capitani Donatella, Mazzoleni Paolo, Proietti Noemi, Raneri Simona, Longobardo Ugo, Di Tullio Valeria (2016). <sup>13</sup>C Solid State Nuclear Magnetic Resonance and  $\mu$ -Raman Spectroscopic Characterization of Sicilian Amber. APPLIED SPECTROSCOPY, vol. 70, p. 1346-1355, ISSN: 0003-7028, doi: 10.1177/0003702816654087 - **Articolo in rivista**
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18. LAZZARINI R, MORETTI S, ORECCHIA S, BETTA PG, PROCOPIO A, A. CATALANO (2008). Enhanced antitumor therapy by inhibition of p21waf1 in human malignant mesothelioma. *CLINICAL CANCER RESEARCH*, vol. 14, p. 5099-5107, ISSN: 1078-0432 - **Articolo in rivista**
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## 6. Hindex of associated investigators (only for the scientific fields in which the use of the H-index is usually adopted)

n°	Surname Name	H-Index	Source
1.	RANERI Simona	5	Scopus
2.	BALLIRANO Paolo	22	Scopus
3.	PROCOPIO Antonio Domenico	45	Scopus
4.	BASSI Anna Maria	18	Scopus
5.	OTTAVIANI Maria Francesca	35	Scopus

**7. Main staff involved (max 10 professors/researchers for each research unit, in addition to the PI or associated investigator), highlighting the time commitment expected**

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**List of the Research Units**

**Unit 1 - GUALTIERI Alessandro**

**Personnel of the research unit**

n°	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	GUALTIERI Alessandro	Professore Ordinario	Università degli Studi di MODENA e REGGIO EMILIA	alessandro.gualtieri@unimore.it	1,2
2.	VEZZALINI Maria Giovanna	Professore Ordinario	Università degli Studi di MODENA e REGGIO EMILIA	mariagiovanna.vezzalini@unimore.it	0,1
3.	LUSVARDI Gigliola	Professore Associato confermato	Università degli Studi di MODENA e REGGIO EMILIA	gigliola.lusvardi@unimore.it	0,1
4.	MALAVASI Gianluca	Professore Associato (L. 240/10)	Università degli Studi di MODENA e REGGIO EMILIA	gmalavasi@unimo.it	0,1
5.	MENABUE Ledi	Professore Ordinario	Università degli Studi di MODENA e REGGIO EMILIA	ledi.menabue@unimore.it	0,1
6.	ZANNINI Paolo	Professore Associato confermato	Università degli Studi di MODENA e REGGIO EMILIA	paolo.zannini@unimore.it	0,1
7.	ARLETTI Rossella	Professore Associato (L. 240/10)	Università degli Studi di TORINO	rossella.arletti@unito.it	0,1

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**Unit 2 - RANERI Simona**

**Personnel of the research unit**

n°	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	RANERI Simona	Ricercatore a t.d. - t.pieno (art. 24 c.3-a L. 240/10)	Università di PISA	SIMONA.RANERI@UNIFI.IT	0,2
2.	LEZZERINI Marco	Professore Associato (L. 240/10)	Università di PISA	lezzolini@dst.unipi.it	0,1
3.	PERCHIAZZI Natale	Professore Associato confermato	Università di PISA	natale.perchiazzi@unipi.it	0,1

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**Unit 3 - BALLIRANO Paolo**

**Personnel of the research unit**

n°	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	BALLIRANO Paolo	Professore Ordinario (L. 240/10)	Università degli Studi di ROMA "La Sapienza"	paolo.ballirano@uniroma1.it	1,1
2.	GIANFAGNA Antonio	Professore Associato confermato	Università degli Studi di ROMA "La Sapienza"	antonio.gianfagna@uniroma1.it	0,1
3.	DE VITO Caterina	Ricercatore confermato	Università degli Studi di ROMA "La Sapienza"	caterina.devito@uniroma1.it	0,1
4.	MIGNARDI Silvano	Ricercatore confermato	Università degli Studi di ROMA "La Sapienza"	SILVANO.MIGNARDI@UNIROMA1.IT	0,1
5.	BLOISE Andrea	Ricercatore confermato	Università della CALABRIA	andrea.bloise@unical.it	0,1

#### Unit 4 - OTTAVIANI Maria Francesca

##### Personnel of the research unit

n°	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	OTTAVIANI Maria Francesca	Professore Ordinario (L. 240/10)	Università degli Studi di Urbino Carlo Bo	maria.ottaviani@uniurb.it	1,0
2.	MATTIOLI Michele	Ricercatore confermato	Università degli Studi di Urbino Carlo Bo	michele.mattioli@uniurb.it	0,1
3.	FORMICA Mauro	Professore Associato (L. 240/10)	Università degli Studi di Urbino Carlo Bo	mauro.formica@uniurb.it	0,1
4.	SANTI Patrizia	Ricercatore confermato	Università degli Studi di Urbino Carlo Bo	patrizia.santi@uniurb.it	0,1
5.	DELLA VENTURA Giancarlo	Professore Ordinario	Università degli Studi ROMA TRE	giancarlo.dellaventura@uniroma3.it	0,1

#### Unit 5 - BASSI Anna Maria

##### Personnel of the research unit

n°	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	BASSI Anna Maria	Ricercatore confermato	Università degli Studi di GENOVA	anna.maria.bassi@unige.it	1,3
2.	CILIBERTI Rosagemma	Professore Associato confermato	Università degli Studi di GENOVA	rosellaciliberti@yahoo.it	0,1
3.	MARENGO Barbara	Ricercatore a t.d. - t.pieno (art. 24 c.3-a L. 240/10)	Università degli Studi di GENOVA	Barbara.Marengo@unige.it	0,1
4.	SCARFI' Sonia	Professore Associato (L. 240/10)	Università degli Studi di GENOVA	soniascarfi@unige.it	0,1
5.	TRAVERSO Nicola	Professore Associato confermato	Università degli Studi di GENOVA	ntravers@medicina.unige.it	0,1
6.	PENCO Susanna	Ricercatore confermato	Università degli Studi di GENOVA	spenco@medicina.unige.it	0,1

#### Unit 6 - PROCOPIO Antonio Domenico

##### Personnel of the research unit

n°	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	PROCOPIO Antonio Domenico	Professore Ordinario	Università Politecnica delle MARCHE	a.d.procopio@univpm.it	0,3
2.	PUGNALONI Armanda	Professore Associato (L. 240/10)	Università Politecnica delle MARCHE	armanda.pugnaloni@univpm.it	0,1

3. MARZIONI Daniela	Professore Associato (L. 240/10) Università Politecnica delle MARCHE	d.marzioni@univpm.it	0,1
4. FAZIOLI Francesca	Professore Associato confermato Università Politecnica delle MARCHE	fazioli@univpm.it	0,1
5. DOUBLIER Sophie	Ricercatore confermato Università degli Studi di TORINO	sophie.doublier@unito.it	0,1

### 8. Major new contracts for staff specifically to recruit

n°	Associated or principal investigator	Number of contracts RTD expected	Number of research grants expected	Number of PhD expected	Predictable overall time commitment (months)
1.	GUALTIERI Alessandro	0	2	1	50
2.	RANERI Simona	1	0	0	24
3.	BALLIRANO Paolo	0	0	0	12
4.	OTTAVIANI Maria Francesca	0	1	0	12
5.	BASSI Anna Maria	0	1	0	12
6.	PROCOPIO Antonio Domenico	0	2	0	24
	<b>Total</b>	<b>1</b>	<b>6</b>	<b>1</b>	<b>134</b>

### 9. Statement by the Principal Investigator

Con la sottomissione della presente proposta, consapevole della responsabilità civile e penale, attesto l'assenza di duplicazione degli obiettivi e dei contributi richiesti con altri progetti in corso o già conclusi

"I dati contenuti nella domanda di finanziamento sono trattati esclusivamente per lo svolgimento delle funzioni istituzionali del MIUR. Incaricato del trattamento è il CINECA - Business Unit MIUR. La consultazione è altresì riservata agli atenei e agli enti di ricerca (ciascuno per le parti di propria competenza), al MIUR - D.G. per il Coordinamento e lo Sviluppo della Ricerca - Ufficio V, al CNR e ai CdS. Il MIUR potrà anche procedere alla diffusione dei principali dati economici e scientifici relativi ai progetti finanziati".

Date 26/03/2018 ore 18:15