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1 **Journal of Toxicology and Environmental Health, Part B**

2
3 **FIVE YEARS UPDATE ON RELATIONSHIPS BETWEEN MALIGNANT PLEURAL**
4 **MESOTHELIOMA AND EXPOSURE TO ASBESTOS AND OTHER ELONGATED**
5 **MINERAL PARTICLES**

6
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1 ABSTRACT

2 Despite the reduction of asbestos worldwide consumption and production due to the ban or
3 restriction of asbestos uses in more than 50 countries since the seventies, malignant
4 mesothelioma remains a disease of concern. Asbestos is still used, imported and exported in
5 several countries, and the number of mesothelioma deaths may be expected to increase in the
6 next decades in these countries. Asbestos exposure is the main risk factor for malignant pleural
7 mesothelioma, but other types of exposures are linked to the occurrence of this cancer. Although
8 recent treatments improve the quality of life of patients with mesothelioma, malignant pleural
9 mesothelioma remains an aggressive disease. Recent treatments have not resulted in appreciable
10 improvement in survival, and then the development of more efficient therapies is urgently
11 needed. The development of novel therapeutic strategies is dependent on our level of knowledge
12 of the physiopathological and molecular changes that mesothelial cells acquired during the
13 neoplastic process. During the past five years, new findings have been published on the etiology,
14 epidemiology, molecular changes and innovative treatments of malignant pleural mesothelioma.
15 This review aims to update the results of recent researches developed on the first three topics. It
16 will focus on the attributable risk of asbestos exposure in men and women, on co-exposure to
17 other minerals and other elongated mineral particles or high aspect ratio nanoparticles. Recent
18 data obtained on genomic and gene alterations, pathways deregulations, and predisposing factors
19 are summarized.

20

1 INTRODUCTION

2

3 After the early recognition of the occurrence of lung fibrosis and cancer in workers
4 occupationally exposed to asbestos fibers (Cooke 1924; Doll 1955; Sebastien et al. 1975;
5 Selikoff, Churg, and Hammond 1964; Simson 1928), and the discovery of the relationship to
6 malignant mesothelioma (Wagner, Sleggs, and Marchand 1960), numerous epidemiological and
7 experimental studies were developed to document the relationships between asbestos exposure
8 and human thoracic malignancies, such as lung cancer and malignant pleural mesothelioma.
9 However, from the middle/end of the 20th century, research has shown that asbestos fibers are not
10 the only type of mineral elongated particles responsible for lung and pleural fibrosis and cancer,
11 in particular malignant mesothelioma. Human exposure to other natural mineral fibers has been
12 associated to malignant mesothelioma, such as erionite, fluoro-edenite, winchite, richterite and
13 tremolite (IARC 2012; Grosse et al. 2014; Dunning et al. 2012). Exposures to irradiation and
14 SV40 virus as co-factor have been also implicated in the development of malignant mesothelioma
15 (Chirieac et al. 2013; Farioli et al. 2013; Jasani and Gibbs 2012).

16

17 With the decrease in asbestos uses, some man-made mineral fibers have replaced these natural
18 mineral fibers, especially mineral wool, glass fibers, and refractory ceramic fibers (RCFs),
19 leading to the development of epidemiological studies in populations exposed to these fibers.
20 IARC classified some man-made fibers (special-purpose fibers and RCFs) as carcinogenic in
21 experimental animals, but lacking of epidemiological data; these fibers were classified in the 2B
22 group, as possibly carcinogenic to humans. These researches were situated in the landscape of
23 investigations developed to understand the health effects resulting from exposure to asbestos
24 fibers and other elongated mineral particles (EMPs) (NIOSH 2011). More recently, with the
25 development of nanotechnologies, including carbon nanotubes, the historical of asbestos diseases
26 allowed to propose that high aspect ratio nanoparticles (HARNs) have a special cancer potential
27 to the lungs and mesothelium, and to develop a paradigm for hazard assessment (Aschberger et
28 al. 2010; Donaldson and Poland 2012; Tran et al. 2011).

29

30 The question of co-exposure is an important challenge to identify and define risk factors. In
31 occupational situations, workers previously exposed to asbestos may have been exposed to

1 replacement fibers, and the potential effects of co-exposures also need to be investigated.
2 Otherwise, to anticipate further issues related to exposure to other EMPs and HARNs, a better
3 knowledge of the mechanism of action and biological signature of fibers, other EMPs and
4 HARNs is needed for regulation and prevention purposes (NIOSH 2011). Moreover, co-
5 exposures to asbestos and silica are also of interest as silica is not known to induce mesothelioma,
6 but joint effects might modify the incidence.

7
8 Mesothelioma arises from the neoplastic transformation of mesothelial cells. For studying the
9 carcinogenic effects of fibers, mesothelioma represents a specific disease, due to its relationship
10 with exposure to mineral fibers. Mesothelioma is linked to past-asbestos exposure in about 80%
11 of the cases. Investigation of physio-pathological changes in mesothelioma, including genomic
12 changes, is of particular interest to link the alterations to the mechanism of action of the fibers.
13 Other extra-thoracic cancers are associated to asbestos exposure, but the link is weaker. A link
14 between asbestos exposure and ovarian cancer is clearly established, based on the study of
15 several strongly positive cohort mortality studies of women with heavy occupational exposure to
16 asbestos, and on a meta-analysis (Bunderson-Schelvan et al. 2011; Camargo et al. 2011; IARC
17 2012; Reid et al. 2013). Moreover, a causal association between asbestos exposure and laryngeal
18 cancer has been also established (IARC 2012; Menvielle et al. 2016; Offermans, Vermeulen,
19 Burdorf, Goldbohm, Kauppinen, et al. 2014). Recently, an association between occupational
20 asbestos exposure and pharyngeal squamous cell carcinoma in men has been also reported
21 (Langevin et al. 2013). Finally, since the last reevaluation of asbestos related cancers by IARC in
22 2012, associations between asbestos exposure and digestive cancers have been reported. Indeed,
23 significant links between mortality due to stomach cancer or oesophagus cancer have been well
24 documented (Offermans, Vermeulen, Burdorf, Goldbohm, Keszei, et al. 2014). For stomach
25 cancer, a meta-analysis reported a meta-Standardized Mortality Ratio (SMR) = 1.15 [95%
26 Confidence Interval (CI): 1.03-1.27] and for oesophagus cancer, the meta-SMR was 1.24 [95%
27 CI: 1.13-1.38], with little evidences of heterogeneity (Fortunato and Rushton 2015; Li, Tang, and
28 Wang 2015). Likewise, the role of asbestos exposure in colorectal cancers remains controversial
29 (Bunderson-Schelvan et al. 2011; Clin et al. 2011; Fang, Le, and Band 2011; IARC 2012). A
30 suggestive relationship for colon cancer incidence was recently found, but with less conclusive
31 results for rectal cancer (Offermans, Vermeulen, Burdorf, Goldbohm, Keszei, et al. 2014).

1
2 Despite the decrease in asbestos production, and asbestos ban in several countries, mesothelioma
3 remains a disease of concern, because of the particularly long latency period between the time
4 since first exposure to asbestos and the onset of the disease with an average of 40 years (30-50
5 years) (Robinson, Musk, and Lake 2005; Rolland et al. 2010). The World Health Organization
6 (WHO) has estimated that mesothelioma, lung cancer, and asbestosis are responsible for about
7 107,000 deaths worldwide (Delgermaa et al. 2011; Kameda et al. 2014; Stayner, Welch, and
8 Lemen 2013). Bang et al. estimated that the importance of premature mortality and loss of
9 potentially productive years of life attributable to asbestos-related diseases were very stable
10 between 1999 and 2010 in United States (Bang et al. 2014). This finding underlies the importance
11 to maintain prevention efforts and to monitor surveillance of asbestos-related diseases temporal
12 trends (Bang et al. 2014). Moreover, the outcome of patients with MPM is poor, long-term
13 survival is rare, with the majority of patients succumbing to their disease within 2 years of
14 diagnosis (Davidson 2015). An increase of only 3 months in overall survival with anti-VEGF and
15 anti-folate therapy has been reported (Zalcman et al. 2015). A strong development of researches
16 to prevent and treat this cancer is needed. In recent years, efforts have been made to improve
17 diagnosis and prognosis, and to design treatments more adapted to the morphological and
18 biological characteristics of the tumors (Musk et al. 2011; Robinson, Musk, and Lake 2005).

19 So far, the histological diagnosis of mesothelioma remains based on 3 predominant subtypes:
20 epithelioid (50 to 60%), sarcomatoid (10 to 20%), biphasic corresponding comprising epithelioid
21 and sarcomatoid components (25 to 35%) and a smaller percentage of desmoplastic forms (1 to
22 2%) (Husain et al. 2013). Well-differentiated papillary mesothelioma is an uncommon form of
23 epithelioid mesothelioma, that is generally a non-invasive tumor with low malignant potential
24 and that occurs mostly in women in the peritoneum, but also in pleura, pericardium, and tunica
25 vaginalis. Some rare cases of well-differentiated papillary mesothelioma with invasive foci are
26 now recognized as stressed in several publications (Churg et al. 2014; Galateau-Salle et al. 2004).

27 Recent biological studies of cancers allow the identification of biomarkers, and benefit of high
28 throughput cell biology technologies, so-called “omics researches”, that permit to characterize the
29 genetic, metabolic and physiological changes linked to cancer. In this area of researches, new
30 findings have been recently reported on mesothelioma.

31

1 The aim of the present work was to summarize the literature data published during the last five
2 years, focusing on epidemiology of malignant pleural mesothelioma (MPM), with special interest
3 to data on co-exposure to asbestos and other fibers, and to silica. Recent advances in our
4 knowledge on the biology of mesothelioma will be summarized. They concern the genetic and
5 epigenetic alterations of the tumor, and possible links to asbestos, and their impact in the
6 treatment of mesothelioma. At the cell level, some new data are related to the deregulation of
7 signaling pathways, and stemness-related features of tumor cells.

1 HUMAN EXPOSURE TO ASBESTOS AND OTHER EMPs AND MALIGNANT 2 MESOTHELIOMA

3
4 In this review, asbestos refers to the natural minerals that are considered in industries and used in
5 experimental-related studies devoted to the investigation of the pathological effects of asbestos.
6 Asbestos is the commercial name given to a family of natural silicate mineral fibers; it refers to
7 the 6 commercial types of asbestos (two varieties: feathery serpentines (chrysotile), and long and
8 thin fibers of amphiboles (crocidolite, amosite, anthophyllite, tremolite and actinolite)) (Case et
9 al. 2011). According to WHO methodology, fibers are defined as particles thinner than $3\mu\text{m}$,
10 longer than $5\mu\text{m}$ and of aspect-ratio >3 . An EMP is an elongated mineral particle thinner than
11 $3\mu\text{m}$, longer than $5\mu\text{m}$ and of aspect-ratio >3 , independently of its chemistry. Then asbestos
12 fibers are also EMP. Other non-asbestiform, non-commercial amphiboles, as found in the
13 vermiculite mines in Libby, such as winchite, richterite and tremolite, are EMP as far as their
14 dimensions correspond to the definition. There is evidence to support the association between
15 exposure to these fibers and the occurrence of asbestos-related diseases, especially nonmalignant
16 pleural abnormalities, lung cancer, and malignant mesothelioma (Antao, Larson, and Horton
17 2012; Carlin et al. 2015).

18 19 **Recent epidemiological advances linked to asbestos exposure**

20
21 Mesothelioma is mainly attributable to occupational or environmental asbestos exposure. All
22 forms of asbestos fibers are carcinogenic to human, and both pleural and peritoneal
23 mesotheliomas are associated with asbestos exposure (IARC 2012). Despite ban of asbestos in
24 some countries, and decline of worldwide production and use of asbestos, these minerals still
25 represent a health problem (Stayner, Welch, and Lemen 2013). Asbestos consumption is
26 increasing in other parts of the world such as India and much of Asia. Since recent publications
27 have reviewed epidemiological data on asbestos exposure, we did not make a
28 comprehensive review of the relevant literature, but instead summarized the main findings
29 reported in these reviews. Briefly, in a worldwide literature review, all types of asbestos fibers
30 were found to cause mesothelioma, including chrysotile (Kanarek 2011). Another review
31 examining the patterns of asbestos exposure (production, export and use) and of asbestos-related

1 diseases concluded that all forms of asbestos fibers are carcinogenic to humans (Frank and Joshi
2 2014). The potency of the different fiber types for lung cancer risk was recently discussed, and
3 authors have questioned the already reported and accepted potency factors for asbestos-related
4 lung cancer, suggesting that differences might be lower (van der Bij et al. 2013). Toxicological
5 and epidemiological studies on effects of airborne fibers were also considered for risk assessment
6 (Lippmann 2014). This author concluded that the effects are dependent on fiber diameter, length,
7 and biopersistence; biopersistent fibers, thinner than 0.1 μm and longer than 5 μm being the most
8 relevant for mesothelioma (Lippmann 2014). Nevertheless, in an exhaustive review focusing on
9 available information from peer-review publications on the size-dependent pathogenic effects of
10 asbestos fibers reported in experimental *in vivo* and *in vitro* studies, fibers shorter than 5 μm were
11 less pathogenic than fibers longer than 5 μm , but the cut-off of 5 μm as the limit for length is
12 used for metrological analyses using light microscopy and is not based on scientific evidence
13 (Boulangier et al. 2014)

14

15 ***Occupational exposure to asbestos***

16

17 Because of their specific chemical and physical properties asbestos fibers have been used in a
18 variety of building construction materials and in a wide range of manufactured goods (IARC
19 2012). Early investigations on asbestos health effects concerned workers in the production and
20 handling of asbestos products. Over the last decades, a shift has been observed in the exposure
21 history of MPM cases, from primary asbestos workers (handling raw asbestos material) to end-
22 users often exposed when installing asbestos products or handling asbestos materials that are still
23 in place (Scherpereel et al. 2010). Elevated risks of MPM were found in sheet-metal workers,
24 plumbers, metal molders, welders, core-makers, cabinetmakers and firefighters, and in the
25 industries of construction, shipbuilding, manufacturing of metal products, chemicals, and railroad
26 and aircraft equipment (Pukkala et al. 2014; Rolland et al. 2010).

27 An English case-control study estimates lifetime risks for British-born male in the 1940s with
28 ≥ 10 years of asbestos exposure before the age of 30 years-old. Lifetime risks were estimated at
29 5.9% for carpenters, 2% for electricians, plumbers and painters, 0.8% for other construction
30 workers, 1.8% for other recognized high-risk occupations and 0.6% in other industries where
31 asbestos may be encountered (Rake et al. 2009). Otherwise, a British cohort study did not find

1 sufficient evidence that greater intensity asbestos exposures would lead to shorter mesothelioma
2 latencies (Frost 2013).

3

4 *Environmental exposure to asbestos*

5

6 MPM is also linked to environmental exposure to asbestos, either in areas of the world where
7 asbestos (generally tremolite) exists as a geological component of the soil (Corsica in France,
8 Cyprus, Turkey, and New Caledonia) or to neighborhood exposures in people living close to
9 asbestos mines or factories, such as the residents of Wittenoom, an Australian town near a
10 crocidolite mine, or in Casale Monferrato, an Italian town next to an asbestos cement factory
11 (Baumann et al. 2011; Ferrante et al. 2015; Hillerdal 1999). Residential distances from industrial
12 sources of asbestos and wind conditions have an impact on the risk of developing environmental
13 mesothelioma (Kurumatani and Kumagai 2008; Tarres et al. 2013). Domestic cases are described
14 in households of asbestos workers, mainly because of asbestos exposure via clothes used at work
15 and washed at home (Lacourt et al. 2014).

16

17 *Attributable risk of asbestos exposure for MPM*

18

19 Few studies estimated the attributable risk (AR) of asbestos exposure for MPM (Agudo et al.
20 2000; Aguilar-Madrid et al. 2010; Lacourt et al. 2014; Rake et al. 2009; Spirtas et al. 1994).
21 While for men, AR of occupational asbestos exposure ranged from 83.1% [99% IC: 74.5-91.5] in
22 France to 85% in the United Kingdom (Lacourt et al. 2014; Rake et al. 2009), it was
23 systematically lower in women from 22.5% [95% CI: 3.2-71.7] in the United States to 41.7%
24 [99% CI: 25.3-58.0] in France (Lacourt et al. 2014; Spirtas et al. 1994). Two studies estimated an
25 AR of occupational asbestos exposure without stratifying by sex; it was 62.0% [99% CI: 48.4-
26 75.6] including all probabilities of exposure to asbestos in Spain and 44% in Mexico (Agudo et
27 al. 2000; Aguilar-Madrid et al. 2010).

28 Besides occupational asbestos exposure, the French and UK studies estimated the AR of non-
29 occupational asbestos exposure among subjects never occupationally exposed to asbestos. A
30 difference between men and women still persisted, but the AR was higher in women than in men:
31 in France, the AR among men was 20.0% [99% CI: 33.5-73.5] against 38.7% [99% CI: 8.4-69.0]

1 in women and in United Kingdom, the AR among men was 1.3% against 16% in women (Rake et
2 al. 2009). In total, from 86.4% to 87.3% of male cases and from 38.1% to 64.8% of female cases
3 were attributed to any source of asbestos exposure (Lacourt et al. 2014; Rake et al. 2009). Thus,
4 these recent data highlight that in women, the AR of asbestos exposure for MPM is enhanced
5 when considering only occupational exposure to asbestos, in comparison with both occupational
6 and non-occupational exposures (38.1% vs 64.8%), whereas this AR remains relatively stable in
7 men (86.4% and 87.3%, respectively) (Lacourt et al. 2014). Nevertheless, an unexplained part of
8 AR for MPM in women (about a third) still persists due to weak asbestos exposure, very remote
9 in time of exposure or other still unknown etiological factors.

10 In an exhaustive study of 318 female MPM cases in the French National Mesothelioma
11 Surveillance Program between 1998 and 2009, 4 clusters were identified: occupational exposure
12 to asbestos and man-made vitreous fibers (MMVF) (7.9%); radiation exposure during
13 radiotherapy (12.9%); any asbestos exposure (19.8%); and "non-exposure" characteristics
14 (59.4%) (Camiade et al. 2013).

15

16 *Co-exposures to asbestos and MMVF or silica particles*

17

18 This part of the review of the literature focuses on the joint effect of asbestos and other EMPs,
19 namely, MMVF. Workers previously exposed to asbestos may have been further exposed to other
20 particles. The question of co-exposure is an important challenge to identify and define risk
21 factors. Co-exposures to asbestos replacement fibers are emerging. Co-exposures to silica are
22 also of interest as silica is not known to induce MM but joint effects might modify the incidence
23 of MPM. Then, these associations are also considered here. From cohort studies of workers, the
24 joint effect of asbestos and other particles has not been studied likely due to the small number of
25 observed mesothelioma cases and the availability of exposure data for both asbestos and other
26 mineral particles.

27 From case-control studies, only 3 population-based studies (Germany, Canada and France)
28 attempted to study the joint effect of occupational asbestos exposure and other mineral particles
29 (Lacourt et al. 2013; Lacourt et al. 2014; Pintos et al. 2009; Rodelsperger et al. 2001). In the three
30 studies, all cases were incident and histologically confirmed male cases. Whereas occupational

1 asbestos exposure and MMVF exposure were retrospectively assessed by expertise in the German
2 and Canadian study, job-exposure matrices were used in the French study.

3 The German study included 125 cases and 125 controls recruited from Hamburg between 1988
4 and 1991 (Rodelsperger et al. 2001). Whereas odds ratios (ORs) for subjects only exposed to
5 asbestos and for subjects only exposed to MMVF were 19.8 [95% CI: 4.7-83] and 15.1 [95% CI:
6 1.05-218], respectively, OR increased by a factor of four when subjects were exposed to both
7 asbestos and MMVF (OR=61.3 [95% CI: 12.9-292]). The Canadian study included 35 cases and
8 1,965 control subjects recruited from Montreal between 1979 to 1986 or 1996 to 2001 (Pintos et
9 al. 2009). OR was increased for subjects ever exposed to both asbestos and MMVF (OR=8.0
10 [95% CI: 3.4–18.9]) compared to those only exposed to asbestos (OR=1.2 [95% CI: 0.3-4.3]).
11 While both studies reported a potential synergistic joint effect of asbestos and MMVF, it should
12 be noted that 95% CI were wide and overlapped each other. Besides, the joint effect of asbestos
13 and MMVF was studied using an ever vs never exposed indicator for both exposures. Thus, the
14 increased OR observed for subjects exposed to both asbestos and MMVF may be due to
15 confounding by asbestos exposure. The cumulative asbestos exposure may be higher in subjects
16 exposed to both asbestos and MMVF compared to subjects only exposed to asbestos leading to an
17 artificially increased OR. In the Canadian study, authors further adjusted for the duration of
18 asbestos exposure in their models but results were unchanged.

19 To account for confounding by asbestos exposure, the French study conducted analysis looking at
20 the dose response relationship between occupational asbestos exposure and MPM in the presence
21 or absence of additional exposure to mineral wool, crystalline silica or refractory ceramic fibers
22 (Lacourt et al. 2013; Lacourt et al. 2014). This study included 1,199 cases and 2,379 controls
23 recruited from several districts of France between 1987-1996 and 1998-2006. Authors
24 systematically reported that the effect of occupational asbestos exposure was increased in
25 presence of a co-exposure. When considering the entire dataset, for subjects occupationally
26 exposed only to asbestos between 1 to 10 fibers/ml.yrs, the OR was 3.7 [95% CI: 2.4-5.6]
27 compared to subjects not exposed to asbestos, mineral wool and silica. However, it increased to
28 7.1 [95% CI: 5.0-10.1], 8.9 [95% CI: 4.5-17.6] and 10.3 [95% CI: 7.0-15.0] when subjects were
29 additionally exposed to mineral wool, silica or to the three mineral particles respectively
30 (Lacourt et al. 2013). When restricting the dataset to subjects ever exposed to asbestos (988 cases
31 and 1,125 controls), the OR for subjects occupationally exposed only to asbestos at 50 fibers/ml-

1 yrs was 1.9 [95% CI: 1.4-2.5] and was 12.8 [95% CI: 4.7-35.1] when subjects were additionally
2 exposed to refractory ceramic fibers (Lacourt et al. 2014). While the issue of the joint effect of
3 asbestos and other mineral particles should be further explored, from the actual literature, the
4 hypothesis of a synergistic joint effect should be considered.

5 6 *Association between pleural plaques and MPM or lung cancer*

7
8 Pleural plaques are benign fibrotic lesions thickening parietal or diaphragmatic pleura, composed
9 of avascular and acellular collagen connective tissue. Pleural plaques are mostly linked to past
10 asbestos exposure. Recently, a follow-up study from the French Asbestos-Related Diseases
11 Cohort (ARDCO), based on a screening Program for Asbestos-Related Diseases in asbestos-
12 exposed male subjects (n = 5,287), reported a strong association between the occurrence of MPM
13 and pleural plaques detected by CT scan (unadjusted hazard ratio (HR) = 8.9 [95% CI: 3.0-26.5];
14 adjusted HR = 6.8 [95% CI: 2.2-21.4] after adjustment for time since first exposure and
15 cumulative exposure index to asbestos). The results of this study suggest that pleural plaques are
16 an independent risk factor of MPM (Pairon et al. 2013). More recently, a significant association
17 between pleural plaques and lung cancer mortality was reported after adjustment for smoking
18 status and asbestos exposure in this same cohort among 1,118 subjects (20.7%) with pleural
19 plaques after 6-year follow-up (Pairon et al. 2014).

20 21 **Human exposure to other EMPs and MPM**

22 23 *Amphiboles, other than asbestos*

24
25 Asbestos is not the only EMP associated to an enhanced risk of mesothelioma development.
26 Other amphiboles (winchite and richterite, so-called “Libby amphiboles”) found in vermiculite
27 mines in Montana (USA) induce mesothelioma in human, and show biological actions, in animals
28 and cultured cells, similar to asbestos fibers (Cyphert et al. 2012; Dunning et al. 2012; Hillegass
29 et al. 2013; Kodavanti et al. 2014). In a recent publication, an elevated percentage of
30 mesothelioma in women, and individuals younger than 55 years, was reported in Southern
31 Nevada, as due to environmental exposure to amphiboles (Baumann, Buck, et al. 2015). In these
32 areas, several types of amphiboles were found, as in Libby (winchite, richterite and tremolite), as

1 well as actinolite) (Baumann, Buck, et al. 2015). Elsewhere, an excess of mesothelioma has been
2 observed in iron ore miners in Northeastern Minnesota, where mining and processing of taconite
3 iron ore generate non-asbestos EMP of undefined type (Lambert et al 2016). Fluoro-edenite is an
4 endemic natural amphibole fiber present in Biancavilla soil in Sicilia (Italy) and also present in
5 the major quarry from which building materials have been extensively extracted. The risk
6 estimated of incidence of MPM in Biancavilla town is higher than in the Sicilian region (Biggeri
7 et al. 2004; Bruno et al. 2014; Comba, Gianfagna, and Paoletti 2003). Recently, a probable link
8 between the presence of pleural plaques and exposure to fluoro-edenite fibers in subjects not
9 exposed to asbestos has been reported through residing in Biancavilla and through their
10 occupation (Rapisarda et al. 2015). IARC classified fibrous amphibole fluoro-edenite as
11 carcinogenic to humans (Group 1) (Grosse et al. 2014).

12

13 *Erionite*

14

15 Erionite belongs to another group of natural minerals, the zeolite group. It is endemic in Turkey
16 and western United States, also strongly associated with the risk of development of mesothelioma
17 (Carbone et al. 2011; Jasani and Gibbs 2012). Recently, erionite has been also localized in
18 Central Mexico and associated to a high risk of mesothelioma and lung cancer (Ortega-Guerrero
19 et al. 2015).

20

21 *Synthetic vitreous fibers*

22

23 Synthetic vitreous fibers (SVF) are subdivided into glass wool, rock wool, slag wool, refractory
24 ceramic fibers and other special-purpose fibers. The IARC classification of SVF was based on
25 chronic inhalation and intra-tracheal instillation studies of special-purpose glass fibers resulted in
26 significant increases of MPM in rats and hamsters. Insulation glass wool, continuous glass
27 filament, rock (stone) wool and slag wool are not classifiable as to their carcinogenicity to
28 humans (Group 3) (IARC 2002). Recently, the existence of little epidemiologic and toxicological
29 evidence concerning a potential link between SVF exposure and risk of mesothelioma occurrence
30 was reported (Boffetta et al. 2014). RCFs have a carcinogenic potency in animals, causing lung
31 cancer and mesothelioma (IARC 2002). In epidemiological studies, a significant association has

1 been previously reported, with the occurrence of pleural plaques detected on chest X-ray, but no
2 significant link was established between MPM and RCF exposure in humans (Lockey et al. 1996;
3 Lockey et al. 2002). According to our knowledge, no new epidemiological data is available.
4 Presently, the link between respiratory cancers occurrence and SVF exposure is still unclear, but
5 some fibers may have characteristics able to induce pathogenic effects (Greim et al. 2014;
6 Lippmann 2014).

7

8 ***Other elongated nanoparticles (Carbon nanotubes, carbon nanofibers, tubular clays)***

9

10 The health effects of other types of HARNs, carbon nanotubes (CNTs), carbon nanofibers
11 (CNFs) and nanotubular clays are a present subject of researches (Genaidy et al. 2009; Jaurand
12 2015; Kayat et al. 2011; Lecouvet 2015). Numerous studies were recently performed to
13 investigate the health effects of CNTs. CNTs are new technological material receiving a large
14 range of industrial and biomedical applications due to their particular electronic and mechanical
15 properties (Kayat et al. 2011; Aschberger et al. 2010; Shvedova et al. 2009; Tran, Zhang, and
16 Webster 2009; Upadhyayula et al. 2009). Industrial and economic development of
17 nanotechnology requires the political and scientific communities to consider issues relating to
18 safety of these materials (Fatkhutdinova, Khaliullin, and Shvedova 2015; Jaurand and Jean 2016).
19 CNTs belong to the category of HARNs, with diameters less than or equal to 100 nanometers,
20 and length that may reach several dozen of micrometers. There are several classes of CNTs,
21 single-walled, double-walled and multi-walled carbon nanotubes. The main route of human
22 occupational exposure is suggested to be inhalation and dermal contact, but environmental
23 exposure could occur regarding the uses of CNTs (Aschberger et al. 2010; Tran, Zhang, and
24 Webster 2009). The ecotoxicological impact of CNTs is also of concern (Upadhyayula et al.
25 2009). Presently, there is no epidemiological data on the effects of CNTs on human health.
26 Experimental studies are available, showing that some CNTs may have biological effects similar
27 to asbestos (cellular damage, pulmonary inflammation, genotoxicity) (Genaidy et al. 2009;
28 Jaurand 2015; Kayat et al. 2011). A recent IARC monograph reviewed the literature on the
29 toxicological effects of CNTs. One type of multi-walled CNTs (MWCNT-7) was classified as
30 possibly carcinogenic to humans (Group 2B), and single-walled CNTs and multi-walled CNTs

1 excluding MWCNT-7 as not classifiable as to their carcinogenicity to humans (Group 3) (Grosse
2 et al. 2014).

3 Other naturally occurring minerals of nanotubular structure, such as the natural clay minerals,
4 halloysite and imogolite, are used in many industrial applications (Vahedi and Pasbakhsh 2015).
5 Halloysite forms multi-layered hollow cylinders and imogolite forms single walled tubes.
6 Halloysite has been used commercially in ceramics and potteries, and as reinforcing agents. Due
7 to their properties, these aluminosilicate nanotubes have potential applications in catalysis,
8 molecular separation, and as loading agents in polymers. Both have potential applications in the
9 area of drug delivery systems and nanobiomedicine (Abdullayev and Lvov 2011; Rapisarda et al.
10 2015). They can be used as unmodified or surface-modified depending on their uses. A few
11 studies have investigated the toxicity of naturally occurring clays. So far, halloysite nanotubes do
12 not appear to exert a cytotoxic effect while some imogolite nanotubes may be cytotoxic and
13 genotoxic. However, due to the insufficient number of studies and wide diversity of the
14 nanotubes it is not possible to draw conclusions on their potential impact on human health
15 (Jaurand In press; Maisanaba et al. 2015).

16

17 **RECENT ADVANCES IN OUR KNOWLEDGE ON THE MOLECULAR BIOLOGY OF**

18 **MALIGNANT MESOTHELIOMA**

19 **Genomic alterations in MPM**

20

21 The genes with the highest frequency of genetic alteration in MPM are *CDKN2A* (cyclin-
22 dependent kinase 2A), *NF2* (neurofibromin type 2) and *BAP1* (BRCA1 (breast cancer 1)-
23 associated protein 1) tumor suppressor genes (COSMIC v2,
24 <http://cancer.sanger.ac.uk/cosmic>) (Forbes et al. 2015).

25 The first two are known for a long time, but recurrent somatic mutations in *BAP1* gene were
26 more recently identified (Bott et al. 2011). *BAP1* is a tumor suppressor gene located on 3p21, a
27 chromosome region frequently lost in mesothelioma (Jean et al. 2012). The percentage of *BAP1*
28 mutations in sporadic MPM reported in the literature depended on the method of analysis; most
29 of sequencing methods did not allow detection of large deletion in tumor samples due to the
30 presence of normal contaminated cells. The percentage of mutations in tumor samples was 20-
31 23%, as determined by Sanger sequencing (Testa et al. 2011; Zauderer et al. 2013). Bott et al.

1 found 42% *BAP1* loss or mutation in primary mesothelioma by integrated genomic analysis and
2 FISH (Fluorescence In Situ Hybridization) (Bott et al. 2011). Higher rate (61%) was reported in
3 DNA isolated from cultures of mesothelioma tumors, in a Japanese study using Sanger
4 sequencing, array CGH (Comparative Genomic Hybridization) and real-time polymerase chain
5 reaction (PCR) (Yoshikawa et al. 2012). A similar rate was reported in 22 frozen biopsies of US
6 patients (Nasu et al. 2015). Sanger sequencing detected mutations in DNA in 27% of the cases
7 and a total of 60% was found with further MLPA analysis (Multiplex Ligation-dependent Probe
8 Amplification). These results point out that an integrated approach is required to determine the
9 frequency of *BAP1* genetic alterations in mesothelioma.

10 Inactivation of *CDKN2A*, *NF2* or *BAP1* genes in mice enhance the frequency of mesothelioma
11 after exposure to asbestos, showing that they are driver genes of mesothelial carcinogenesis
12 (Altomare et al. 2011; Fleury-Feith et al. 2003; Xu et al. 2014). *CDKN2A* gene encodes two cell
13 cycle regulators p16^{INK4A} and p14^{ARF}. This gene is located on a locus in 9p21, frequently lost by
14 homozygous deletion in MPM, which also contains the *CDKN2B* gene explaining also the
15 frequent alterations to this later gene (Jean et al. 2011). *NF2* gene encodes the merlin
16 multifunctional protein that plays a role in cell adhesion and regulates many signaling pathways
17 involved in cell proliferation including Hippo pathway. *BAP1* gene encodes a nuclear
18 deubiquitinase particularly involved in transcription regulation and remodeling of chromatin
19 whose functions are not fully known. Other tumor suppressor genes are mutated at lower
20 frequencies in MPM as the well-known *TP53* gene involved in the carcinogenesis of several
21 cancers (COSMIC v2) (Forbes et al. 2015) or the *LATS2* gene (Bott et al. 2011; Murakami et al.
22 2011). *LATS2* gene encodes a serine-threonine kinase that is a member of the Hippo pathway as
23 merlin (*NF2*). Members of other signaling pathways have mutation in MPM, such as the
24 hedgehog pathway, but at a lower frequency than Hippo pathway (Lim et al. 2013).

25 In contrast to tumor suppressor genes, oncogene mutations are infrequent in MPM. Mutations in
26 *KRAS*, *BRAF*, *EGFR* and *PIK3CA* genes have been described earlier in the literature and the low
27 frequency rate of mutation was confirmed by recent studies (Mezzapelle et al. 2013; Schildgen et
28 al. 2015; Shukuya et al. 2014). Oncogenic recurrent mutations in the *TERT* promoter were also
29 identified at a low frequency, but are strongly associated with sarcomatoid MPM. These
30 mutations are involved in the overexpression of the gene encoding the catalytic subunit of
31 telomerase (Tallet et al. 2014).

1 There are only few NGS (Next Generation Sequencing) data for MPM. Recently, the *CUL1* gene,
2 a component of an ubiquitin ligase, was suggested as a driver gene for mesothelial
3 carcinogenesis, as the frequency of damaging *CUL1* mutations was greater than the significance
4 threshold expected for driver mutations in an exome sequencing study of 22 MPM (Guo et al.
5 2015). Genetic alterations of member genes of the mSWI/SNF chromatin remodeling complex
6 and of the Hippo pathway, others than *NF2* and *LATS2* genes, were found in another NGS studies
7 of 8 and 16 MPM, respectively (Miyanaga et al. 2015; Yoshikawa et al. 2012). The largest NGS
8 study including 123 formalin-fixed, paraffin-embedded (FFPE) biopsies showed a complex
9 landscape view of the somatic genomic alterations in MPM (Lo Iacono et al. 2015). The pattern
10 of MPM mutation would be clarified with the expected release of TCGA (The Cancer Genome
11 Atlas, <https://tcga-data.nci.nih.gov>) exome data, which included 87 MPM.

12

13 **Genomics of MPM**

14

15 Several omics studies have been conducted on MPM to identify chromosomal alterations,
16 epigenetic modifications and gene expression deregulations.

17 Analyzes of chromosomal alterations in mesothelioma, performed by various techniques, such as
18 cytogenetic analysis of standard karyotype, classical CGH or SNP (single nucleotide
19 polymorphism) arrays, showed that numerous chromosomal abnormalities are associated with
20 MPM. They also resulted in a fairly reliable mapping of the recurrent altered regions (Jean et al.
21 2012; Melaiu et al. 2013). Recently, studies using high-resolution oligonucleotide microarrays
22 allowed to define smaller chromosome regions with biallelic deletion, which are potentially
23 informative about the presence of tumor suppressor genes (Klorin et al. 2013). Spectral
24 karyotyping (SKY) and RNA sequencing identified more precisely chromosome translocations in
25 MPM, whose recurrence remains to be determined (Klorin et al. 2013; Panagopoulos et al. 2013).
26 Methylome analyses by micro-array demonstrated that MPM are characterized by alterations of
27 the global epigenetic profile and show specific patterns of gene methylation as compared to
28 normal pleura or other tumors (Christensen et al. 2009; Goto et al. 2009). Specific DNA
29 methylation profile of MPM could be used as diagnostic and prognostic biomarker (Christensen
30 et al. 2009; Goto et al. 2009), but no precise epigenetic signature was defined since these two
31 initial publications (Vandermeers et al. 2013). However, recent data support the role of an

1 epigenetic mechanism in mesothelial carcinogenesis by identifying new genes or miRNAs acting
2 as tumor suppressors, which are downregulated by DNA methylation (Cheng et al. 2013; Cioce et
3 al. 2014).

4 Transcriptome microarray studies on MPM are quite numerous, more than twenty before 2011.
5 They were carried out either on cultured cell lines either on tumor samples, and generally include
6 few tumor cases, three studies exceeding thirty cases (Gordon et al. 2003; Gordon et al. 2005;
7 Holloway et al. 2006) and one study approaching one hundred cases (Lopez-Rios et al. 2006).
8 These studies mainly focused on the comparison between MPM and normal pleura or mesothelial
9 cells, between histological subtypes of MPM or between MPM and other invasive or
10 metastasizing tumors in the pleura, mainly lung adenocarcinoma. The identified biomarkers were
11 listed in recent reviews (Jean et al. 2012; Melaiu et al. 2012). Given the inconsistency between
12 results of transcriptome studies, large independent series of MPM will be needed to validate
13 specific MPM biomarkers. Recently, expression deregulation of 59 of 119 biomarkers, selected
14 from data mining study combined with a literature review of transcriptomic studies, were
15 validated by RT-qPCR in an independent series of 22 MPM and 20 normal pleura (Melaiu et al.
16 2015). Transcriptomic approaches have a diagnostic interest as demonstrated by gene expression
17 ratio analysis (De Rienzo et al. 2013) and a prognostic interest as shown by older studies, which
18 defined predictors of survival based on gene expression (Gordon et al. 2009; Gordon et al. 2003;
19 Gordon et al. 2005; Lopez-Rios et al. 2006; Pass et al. 2004). These studies also allow to clarify
20 the molecular inter-tumor heterogeneity of MPM. Two older studies classified MPM into
21 subgroups, which correlated with histological types (Gordon et al. 2005; Hoang et al. 2004).
22 Recently, a classification of MPM in three molecular subtypes based on differences in gene
23 expression of 53 tumor samples was proposed with no correlation with clinical or histological
24 characteristics of the tumors (Suraokar et al. 2014). A classification in two molecular subtypes
25 was also defined from 38 cultured MPM primary cell lines and validated using 108 MPM tumor
26 samples. This classification is of interest as it is related partly to histological subtypes and allows
27 to separate epitheloid MPM in two subgroups of different survival outcome (de Reynies et al.
28 2014).

29 In the same way as for the transcriptomic studies, miRNome analyses focused mainly on the
30 differences between MPM and normal tissues or other types of cancer. These studies lead to the
31 identification of several potential MPM diagnosis biomarkers, which were summarized in a

1 recent review (Reid 2015). The differences of miRNA expression between MPM histological
2 subtypes were also considered. MiRNA expression levels may be also good biomarkers for
3 predicting the prognosis as first mentioned in 2010 (Pass et al. 2010) and as investigated in
4 several recent studies (Andersen et al. 2014; Kirschner et al. 2015; Matsumoto et al. 2014). These
5 studies lead to the identification of individual miRNA, which expression is linked to prognosis
6 such as miR-29c-5p, miR-193b or miR-31 or the establishment of predictive signature composed
7 of several miRNAs. However, prognosis value validation of these miRNAs predictors is needed
8 in larger independent MPM cohorts. Interestingly, the use of miRNAs as therapeutic targets is an
9 emerging field in MPM even if the effectiveness of this strategy has been shown for the moment
10 only in preclinical models (Reid et al. 2013; Ueno et al. 2014). There is a clinical trial in progress
11 using miRNA-loaded nanocells, which derived from genetically-modified bacteria, for the
12 delivery of miRNA in mesothelioma (Kao et al. 2015).

13 Integrated multi-omics studies on the same MPM cases should allow to better characterize the
14 molecular features of MPM and to clarify the different pathways of mesothelial carcinogenesis.
15 Unfortunately, integrated multi-omics studies are rare in MPM and incomplete. To our
16 knowledge, only one study combined SNP and methylome arrays to analyze contributions of
17 chromosomal and epigenetic alterations in MPM and revealed a strong association between
18 global gene copy number alterations and global epigenetic dysregulation in MPM, rather than a
19 discrete, local coordination of gene inactivation (Christensen et al. 2010), and two studies linked
20 omic data to the mutation profile of the tumors. Lopez-Rios *et al.* analyzed genetic alterations of
21 the *CDKN2A* gene and performed a transcriptomic study using the same samples, but did not
22 really integrate the result (Lopez-Rios et al. 2006). De Reynies *et al.* compared the distribution of
23 the mutations in the main genes involved in mesothelial carcinogenesis (*CDKN2A*, *NF2*, *BAP1*
24 and *TP53*) in the two transcriptomic MPM subgroups they defined, showing a higher frequency
25 of *BAP1* mutation in the subgroup with the best prognosis (de Reynies et al. 2014). The analysis
26 of TCGA (The Cancer Genome Atlas, <https://tcga-data.nci.nih.gov>) data, which include
27 exome, SNP, methylation, mRNA and miRNA analysis on the same 87 MPM cases, would be a
28 first step toward integrated approaches in MPM. Taking into account genetic and genomic data
29 and also clinical, histological and epidemiological data will open important diagnostic and
30 prognostic prospects and lead to the development of personalized medicine for patients.

31

1 Pathways deregulation

2

3 During the past ten years, genetic and epigenetic studies have increased our understanding of the
4 molecular pathogenesis of MPM. The results demonstrated that multiple signaling pathways are
5 altered in mesothelioma. Alterations in cell cycle regulation were first detected by the deletion of
6 genes at the *INK4* locus (Xio et al. 1995). The Hippo pathway was further identified due to the
7 inactivation of *NF2* gene (Sekido 2010). Alterations of other regulators of Hippo pathway, *LATS1*
8 and *LATS2* and *SAV1*, and the overexpression of the transcription cofactor YAP have been
9 reported in some MPM (Jaurand and Jean 2016). Deregulation of this pathway can also occur via
10 the inhibition of merlin phosphatase, MYPT1-PP1 δ , by protein kinase C-potentiated phosphatase
11 inhibitor (CPI-17), which is frequently overexpressed in MPM, leaving merlin in a
12 phosphorylated inactive form (Petrilli and Fernandez-Valle 2015; Thurneysen et al. 2009). Loss
13 of merlin could also lead to activate the E3 ubiquitin ligase, CRL4(DCAF1), which is inhibited
14 by its binding to the active, growth-inhibitory form of merlin in the nucleus (Petrilli and
15 Fernandez-Valle 2015).

16 Further studies have documented changes in the regulation of other pathways, from mutations in
17 key members and/or their differential expression in comparison to normal mesothelial cells. A
18 number of studies have emphasized the role of receptor tyrosine kinases (RTKs), which
19 activation leads to constitutive upregulation of two major downstream cell signaling cascades
20 involved in many regulations, including cell growth and survival i.e. Raf/MEK-extracellular
21 signal-regulated kinase and phosphoinositide-3 kinase (PI3K/AKT), and the mTOR downstream
22 signaling (Jaurand and Jean 2016; Jean et al. 2012; Sekido 2013). Our knowledge on the
23 deregulated pathways is increasing. Hedgehog pathway seems activated in MPM, possibly due to
24 mutations in members, receptors or regulators of the pathway such as PTCH1, SMO and SFU, and
25 its activation is associated with the worst clinical outcome (Felley-Bosco and Stahel 2014).
26 Several members of the WNT pathway have been reported as deregulated in MPM relative to
27 mesothelial cells, by the overexpression of agonists (WNTs, Dvl) or down regulation of
28 antagonists (SFRP4, WIF-1, Dvl) providing evidence for altered expression of a number of
29 Wnt/Fzd signaling molecules in MPM (de Assis, Locatelli, and Isoldi 2014; Fox et al. 2013;
30 Jaurand and Jean 2016; Pohl et al. 2015).

31

1 **Stem cells**

2 Using side-population isolation or selection of tumor initiating cells, some studies have identified
3 populations of mesothelioma cells that express several putative cancer stem cell (CSC) markers
4 such as CD9, CD24, and CD26, ABCG2, OCT4/POU5F1 and nestin (Ghani et al. 2011; Pasdar et
5 al. 2015; Thies et al. 2015). These cells have interest as targets for pharmacological novel anti-
6 tumor drugs (Favoni et al. 2012). Further researches will likely be developed to better define the
7 characteristics of the cell types present in the tumor; more particularly their stemness
8 characteristics.

9 Recently, one study suggested that MPM originate as polyclonal tumors based on the methylation
10 status of the polymorphic human androgen receptor (*HUMARA*) locus (Comertpay et al. 2014).
11 Future studies including deep whole genome sequencing will precise the natural history of the
12 MPM and the clonal origin of MPM.

13

14 **Predisposing factors**

15

16 The role of factors that influence susceptibility to mineral fiber-induced diseases has been
17 recently reviewed, including age, gender and disease status, genetics, and nutrition as previously
18 reviewed (Below et al. 2011; Toumpanakis and Theocharis 2011). Several studies investigated on
19 polymorphism analyses of genes involved in xenobiotic and oxidative metabolism and DNA
20 repair systems such as, *GSTT1*, *GSTM1*, *NAT2*, *CYP1A1*, *EPHX*, *XRCC1*, *XRCC3*, *RAD50*,
21 *RAD54L* and *RAD21*, but no reproductive and clear-cut result was evidenced (Below et al. 2011;
22 Toumpanakis and Theocharis 2011). According to our knowledge no new findings have been
23 more recently published. However, the knowledge of single nucleotide polymorphism in genes of
24 the DNA repair system is of interest to account for the response to chemotherapy and
25 identification of biomarkers (Frischknecht et al. 2015; Panou et al. 2015; Peters et al. 2014).

26 The familial occurrence of mesothelioma has been observed since the 80's (Dawson et al. 1992).
27 More recently, *BAP1* was shown frequently mutated in several hereditary cancers, uveal
28 melanoma, cutaneous melanomas, basal cell carcinoma and renal cell carcinoma (Murali,
29 Wiesner, and Scolyer 2013). It has been suggested that *BAP1* mutations is implicated in an
30 hereditary cancer predisposition in a small subset of families with uveal melanoma and other
31 cancers, including mesothelioma (Abdel-Rahman et al. 2011). The discovery of *BAP1* germline

1 mutations in two families with a high incidence of mesothelioma was first reported in 2011
2 (Testa et al. 2011). Further DNA sequencing in 26 sporadic MPM demonstrated 2 cases with
3 germline mutations in *BAP1*, previously diagnosed for uveal melanoma. The *BAP1* mutational
4 status was studied in five multiplex families that showed malignant tumor predisposition,
5 including mesothelioma (Betti et al. 2015). Only one family carried a truncating germline
6 mutation suggesting that other genes may be involved in familial MPM predisposition syndrome
7 (Betti et al. 2015). In this study, all patients have been exposed to asbestos, most frequently by
8 household exposure, reported as low, due to occupational exposure of parents (Betti et al. 2015).
9 Recently, germinal DNA sequencing was carried out in sporadic MPM for *BAP1* mutations. All
10 but one DNA showed a wild type sequence in 78 sporadic MPM, by Sanger sequencing (Rusch et
11 al. 2015), and all germline DNAs were wild-type in 22 mesothelioma samples (Nasu et al. 2015).
12 Sanger sequencing and MLPA analyses found no germinal mutation in 103 MPM samples. In an
13 analysis of PubMed databases identifying families studies with germline *BAP1* mutations in
14 mesothelioma (both pleural and peritoneal), and comparing to sporadic cases recorded in the
15 United States Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2010,
16 patients with germline *BAP1* mutations in mesothelioma had a longer survival than without *BAP1*
17 mutation (Baumann, Flores, et al. 2015). Using tissue microarray analyses a prolonged survival
18 was also reported in mesothelioma with *BAP1* loss (Arzt et al. 2014; Farzin et al. 2015)
19 These studies demonstrate that the risk of mesothelioma is influenced by *BAP1* germline
20 alterations, and mesothelioma can develop as a familial cancer syndrome (Sekido 2013).
21 Importantly, the presence of germline *BAP1* mutations in sporadic MPM is very low; showing
22 that mesothelioma induction in asbestos-exposed patients is not a consequence of germline
23 mutation.

24 Immunohistochemistry (IHC) is an accessible method to determine protein expression, useful to
25 diagnosis and prognosis. The results reported in two publications suggest that IHC may be a
26 reliable method to identify *BAP1* mutations as they found a correlation between BAP1 expression
27 and mutations (Andrici et al. 2015; Nasu et al. 2015). Loss of BAP1 determined by IHC is
28 proposed as useful to support the diagnosis of mesothelioma. Loss of BAP1 and/or p16^{INK4A} by
29 IHC in well-identified mesothelial cells was recently considered as useful for cytological
30 diagnosis of mesothelioma, regarding the good correlation between the protein status in a series

1 of 15 pairs biopsies/cytology samples (Hwang et al. 2015). However, further researches with a
2 greater number of cases are necessary to validate these results

3

4 **CONCLUSIONS**

5

6 The relationship between asbestos exposure and the development of MPM is well established,
7 and all epidemiological data have demonstrated that asbestos exposure is found in a large
8 percentage of MPM cases, with a higher risk for men than for women. The calculations of AR
9 show that the risk is much higher for men compared to women, for occupational exposure, while
10 it is the opposite for non-occupational exposures. However, when both types of exposures were
11 associated, the risk in women becomes closer that of men. Additional risk factors (other types of
12 fibers, irradiation) or cofactors (SV40) have emerged. MMVF now appear potential cofactors to
13 increase the risk of MPM. Epidemiological studies should be developed to investigate the risk of
14 multi-exposures associated with asbestos, including low doses, and to other new particles,
15 especially HARNs.

16 Many progresses have been made in our understanding of the biology of MPM and the molecular
17 changes occurring in MPM cells. From recent data, a role of *BAP1* in familial mesothelioma was
18 found, but germline mutations in *BAP1* are infrequent in sporadic mesothelioma. Except an
19 activating mutation in the promoter of *TERT*, somatic mutations have been found in tumor
20 suppressor genes. Overall, the number of genes with recurrent mutations is limited. In contrast,
21 there is a high rate of chromosome aberrations, mainly deletion of chromosome regions, leading
22 to gene copy number alterations; These genomic characteristics may be associated to the
23 mechanism of action of asbestos. Up to now, there is no signature of asbestos in MPM, but more
24 frequent losses in chromosomal 14q11 region were reported in exposed patients (Borczuk et al.
25 2016; Jean et al. 2011). NGS studies should allow to precise the genetic and genomic landscape
26 of MPM mutations. Characterization of the genetic changes in MPM from asbestos-exposed
27 patients would be of interest to better understand the mechanism of action of asbestos and would
28 be useful to study the effects of other EMPs.

29 The integration of “omics” studies should permit to develop a molecular pathophysiological
30 classification of MPM, which in addition to histological classification and clinical criteria should
31 improve diagnosis and therapeutic strategy. Unfortunately, MPM remains an incurable disease.

1 Recent strategies focused on targeted therapies, but the molecular characteristics of the tumors
2 were not tested to determine the relevance of the drug on the basis of the molecular specificities
3 of the tumors and exposure. In the future, this knowledge should improve these new therapeutic
4 options, towards a therapy of precision for MPM.

5 Epidemiological studies have demonstrated that asbestos fibers are not the only carcinogenic
6 natural fibers and that the carcinogenic potency is not limited to amphibole fibers, either asbestos,
7 or non-asbestos. Our knowledge on exposure situations in workers demonstrated that the
8 hypothesis of a synergistic joint effect should be taken into consideration. Co-exposures to
9 asbestos and to some man-made fibers or to silica enhance the risk of mesothelioma. This should
10 be further investigated to better define the risk of mixed exposures that occur both in workers and
11 in the general population. Epidemiological data have also demonstrated that exposure to asbestos
12 and to other amphiboles or to erionite is not limited to occupational situations, but environmental
13 exposures have been linked to the occurrence of mesothelioma. Domestic exposures have been
14 early reported. In these situations, the level of exposure is lower than in workers' exposures. A
15 recent study found a consistent elevated risk of mesothelioma in the domestically exposed
16 populations. Simulations of low-level of chrysotile-exposed workers indicate asbestos levels
17 commensurate with background concentrations in those exposed domestically (Goswami et al.
18 2013).

19 On the basis of the mechanisms of carcinogenicity of asbestos, the biological effects of other
20 particles sharing some dimensional features with asbestos have been considered. Man-made
21 fibers and more recently EMPs are the subject of numerous studies. The current researches
22 benefited of the works on asbestos and led to consider the effects of CNTs. Although the weight
23 of evidence is insufficient, due to the variety of CNTs and limited number of studies for several
24 toxicity endpoints, it was found that some CNTs might pose danger for human health. The
25 development of researches on the molecular characteristics of MPM has a paramount interest for
26 a better classification of MPM, and definition of the different physio-pathological changes
27 specific of the tumors. This identification will permit to develop therapeutic strategies absolutely
28 needed for this orphan disease.

29

30 **Note**

1 During the review process of the manuscript, several relevant papers have been published.
2 Frequent *SETDB1* mutations have been found in MPM (Kang et al. 2016). Otherwise, the genetic
3 landscape of MPM has been specified by reporting recurrent mutations, gene fusions and splicing
4 alterations in a large series of tumor samples (Bueno et al. 2016). A recent trial associating anti-
5 VEGF and anti-folate therapy has increased by three months the overall survival of patients with
6 MPM (Zalcman et al. 2015). Concerning the effects of CNTs, aberrant changes in mRNA and
7 ncRNA (non-coding RNA) expression profiles in the blood of workers, exposed or not exposed
8 to MWCNTs, have been reported (Shvedova et al. 2016).

9

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