Reviewer’s report

Title: Impact of Arsenic, Asbestos and Radon Exposure on the Lung Cancer Genome

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Reviewer: Didier Jean

Reviewer’s report:

This manuscript is a summary review on genetic and epigenetic alterations linked to arsenic, asbestos and radon exposure in lung cancer. It is an interesting topic as few review on this subject are available in the literature. Such bibliographical analysis is needed. Unfortunately, several revisions are necessary to improve the interest of the present review.

• Major Compulsory Revisions

1. One of the major concerns is that the authors did not take into account enough the genetic effect of tobacco smoking, the major risk for lung cancer. When the authors summarize results on epigenetic and genetic effects of arsenic, asbestos and radon on lung cancer, it is not mentioned whether patients were smokers or non-smokers.

2. Another point that needs to be addressed more precisely is the genotoxic mechanisms of these carcinogens. The authors only focus on oxidative stress. Concerning asbestos, generation of reactive oxidative species is certainly involved, but other mechanisms could also explain the genetic and epigenetic effects of asbestos. For example, in cells in culture, asbestos fibers interfere with the mitotic spindle and thereby could induce numerical or structural chromosomal aberrations. Recently, a comprehensive review article, part of the “Asbestos Workshop: A Science-Based Examination of the Mode of Action of Asbestos and Related Mineral Fibers” funded by NIEHS, was published (Huang et al., 2011). In the present review at lines 202-203 page 8, the authors address these issues only briefly and uncompletely. Authors should better describe the mechanism of asbestos carcinogenesis, which is not limited to oxidative stress induction, in page 7 (asbestos mechanism chapter). Consequently, they should modify the figure 3.

3. To illustrate the effects of asbestos, the authors quoted references 135, 142 and 151) that did not deal with lung cancer but with mesothelioma. So far, with the exception of CDKN2A gene locus, genetic alterations are different between these two tumors, indicating that asbestos effect at the genetic level could be cell type specific. The authors need to describe either asbestos effect in lung cancer alone or in both thoracic tumor including mesothelioma, but in a separate chapter.

4. Important data on asbestos genetic effect on lung cancer are missing. Several
studies searched for the signature of asbestos in thoracic cancers. They studied the link between KRAS, TP53 or CDKN2A mutations and asbestos exposure in lung cancers (Wang et al., 1995; Husgafvel-Pursiainen et al., 1999; Nelson et al., 1999; Andujar et al., 2010).

5. The authors should carefully check the genetic alterations in Table 2. For instance, in reference 131, it is shown that 14q11.2 was amplified in non-exposed asbestos patients and not in exposed patients.

• Minor Essential Revisions

1. Concerning some developed countries, several recent epidemiological studies suggest that mesothelioma incidence will not spike between 2020 and 2040, but reach recently a plateau (correction in page 5, lines 99-102).

2. As authors mentioned arsenic remediation, it should be interesting that the authors reported on asbestos remediation, that is under study especially in Italy.

• Discretionary Revisions

1. The sentence “Asbestos fibers are not classical mutagens, since in most cases they are not fully metabolized by the organism and do not interact directly with DNA.” is not appropriate (page 7, line 163). While metabolization is likely for chemical compounds such as PAH, solid compounds such as mineral fibers are unlikely metabolized. Moreover, as mentioned above, asbestos fibers could interact with chromosomes. Then, this sentence should be modified.


3. If Zimbabwe production was banned in 2004, it should not be in yellow in Figure 1 or Authors are confident that asbestos production started again in 2010.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.