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Letter to the Editor: Comments on the paper of Wylie and Korchevskiy – Carcinogenicity of fibrous glaucophane: How should we fill the data gaps?

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ABSTRACT

Assessing the human health risk of mineral fibres is an intricate task. In the recent article by Wylie and Korchevskiy (2021) – Carcinogenicity of fibrous glaucophane: how to fill data gaps? (Curr. Res. Toxicol. Vol. 2, pp. 202–203), the authors discuss the potential toxicity and pathogenicity of fibrous glaucophane from the Franciscan Complex, California (USA). Because most of the points of discussion concerns the mineral fibre toxicity/pathogenicity model developed by our research group and the application to the case of fibrous glaucophane (Gualtieri, 2021, Curr. Res. Toxicol. Vol. 2, pp. 42–52), the aim of this Letter is to clear some basic issues, to fill some information gaps and, with a constructive spirit, to provide a complete picture on this topic.

Dear Editor,

the short communication of Wylie and Korchevskiy (2021) was intended to provide clarifications on the existing data and models developed to assess the toxicity and pathogenicity potential of fibrous glaucophane, an amphibole mineral fibre widespread distributed in the rocks of the Franciscan Complex blueschist facies in California (USA) (Erskine and Bailey, 2018). Both the population living close to glaucophane-rich blueschist outcrops and the workers at the Calaveras Dam Replacement Project (CDRP), where the glaucophane rich rocks are used to build the embankment of the dam, may be exposed to this potential natural hazard. At the CDRP site, methods of dust control, demarcation of regulated areas required by regulations and the selection of personal worker protection, particularly respirators are in use (Erskine and Bailey, 2018). Because many points of discussion regard the application of a recently developed model of toxicity/-pathogenicity of mineral fibres (Gualtieri, 2021) to the case of fibrous glaucophane, this letter is aimed at providing some necessary missing pieces of information and, with a constructive spirit, to deliver a comprehensive picture on this matter.

The model in question attempts to assess the toxicity/pathogenicity potential of mineral fibres (Gualtieri, 2018; Mossman and Gualtieri, 2020) and delivers a Fibre Potential Toxicity/Pathogenicity Index (FPTI) based on all physical/crystal-chemical parameters that induce biological mechanisms responsible for adverse effects *in vivo*. It is intended to be a basic paradigm to predict if a mineral fibre possesses a toxicity/pathogenicity potential when inhaled and hosted in the lung environment, and quantitatively compares its potential to that of other mineral fibres. Gualtieri (2021) pointed out that the adverse effects prompted by mineral fibres leading to toxic/pathogenic mechanisms do not refer to any specific lung disease. The model allows to classify unregulated mineral fibres such as fibrous glaucophane to assess a priori if they are potentially toxic/pathogenic and should be subject to *in vitro/in vivo* toxicity testing. The calculated FPTI value for fibrous glaucophane from Marin County (CA, USA) was 2.77(0.25) (Di Giuseppe et al., 2019). If associated errors are considered, the value is comparable to that of standard UICC crocidolite (2.73(0.18): Di Giuseppe et al., 2019), classified as substance carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC, 2012).

Concerning the specific data gaps on the carcinogenicity of fibrous glaucophane, Wylie and Korchevskiy (2021) used aerosol data collected downwind and just outside the construction area from the Calaveras Dam, to determine the metrics of the glaucophane particles. These data are not directly comparable to our morphometric data that were collected for a sample from Marin County, found more than

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100 km away from the Calaveras dam, and determined on the bulk sample and not from a selected aerosol fraction. Notwithstanding, it should be noted that the size of the fibres from the two localities is not very different because the mean length of the glaucophane particles is 4.00 μm for the sample from Marin County (Di Giuseppe et al., 2019) and 6.94 μm (with ca. 46% of the particles <5 μm) for the sample from the Calaveras Dam (Wylie et al., 2020), respectively.

Wylie and Korchevskiy (2021) pointed out that a significant issue with the FPTI index is the lack of scaling by the observed carcinogenic potential as the index is developed from a set of parameters, which, taken separately, can be seen as predictors of toxicity. FPTI of a mineral fibre relies on a physically/chemically robust *ab initio* model measuring all the fibre-related parameters that induce biological mechanisms responsible for cancer-related adverse effects *in vivo*. The calculated values are compared among the different fibre species and especially the positive standards (the fibres classified as carcinogenic to humans according to the IARC, namely amphibole asbestos) and the negative standards (the fibres not classifiable as to their carcinogenicity to humans according to the IARC). Hence, as reported above, the model predicts if an unregulated fibre displays FPTI values comparable to those of the carcinogenic fibres and consequently should be regarded as a natural hazard. The *ab initio* model is irrespective of all the factors playing a role in the definition of the so-called carcinogenic potential, an empirical parameter based on epidemiological data, like the dose, the type of exposure (working/environmental), the genetic susceptibility and more. Moreover, the carcinogenic potential refers to specific diseases like malignant mesothelioma (MM) while FPTI generically considers pathogenicity in general. For all these reasons, the direct scaling by the FPTI model to observed carcinogenic potential is not possible. It should be remarked that the validity of the empirical models for the determination of the carcinogenic potential must still be proven as the only quantitative methods universally accepted to date to determine the carcinogenicity of substances including mineral fibres are the *in vivo* animal testing (see for example Brody and Overby, 2018) using well established and standardized protocols such as those applied for 40 years by the Italian Ramazzini Institute (Maltoni et al., 2002; Soffritti et al., 2002) of by the state-of-the-art inhalation facility employed by Citoxlab (Bernstein et al., 2020). Besides that, toxicity parameters cannot be taken separately from the adverse effects that specifically induce carcinogenicity as toxicity cannot be separated from pathogenicity, the most relevant example being toxic agents like the reactive oxygen species (ROS) whose chronic generation, overwhelming the antioxidant cell defence, induces alteration of membrane lipids and proteins, cell injury and DNA damage (Mossman, 2018) and is one of the major causes of cancer.

Wylie and Korchevskiy (2021) also remarked that, if FPTI values for crocidolite, amosite, tremolite and crocidolite as published by Gualtieri (2018) would be compared with published mesothelioma potency in the corresponding cohorts of workers, the correlation between the index and potency appears to be not statistically significant, demonstrating the fact that the combination of the parameters in FPTI index has not, in reality, expressed the integral carcinogenicity of mineral particles. FPTI cannot be directly compared to the mesothelioma potency index because: (1) as explained above, FPTI does not express the integral carcinogenicity of mineral particles but predicts the *ab initio* potential toxicity/pathogenicity of mineral fibres without considering the dose-dependency, the type of exposure, the genetic susceptibility of the exposed subjects and other factors that contribute to determine the actual observed carcinogenicity of mineral particles and especially asbestos; (2) mesothelioma potency is not synonym of toxicity/pathogenicity potential. MM is just one of the many diseases due to the exposure of asbestos minerals; (3) FPTI values for crocidolite, amosite, tremolite (Gualtieri, 2018) should not be compared with values of published mesothelioma potency of cohorts of workers because the fibres investigated in our work are not the same as those to which the workers were exposed.

Wylie and Korchevskiy (2021) also remarked that glaucophane, according to our *in vitro* tests (Gualtieri et al., 2021), "apparently induces lower toxic effects compared to crocidolite." As a matter of fact, if the statistics of the errors associated to the values is considered (FPTI value for fibrous glaucophane from Marin County is 2.77(0.25) while the value for standard UICC crocidolite is 2.73(0.18) as reported in Di Giuseppe et al., 2019), the apparent discrepancy between the FPTI prediction and the results of the *in vitro* tests can be well explained. Besides that, as already pointed, FPTI model does not consider only toxicity effects *in vitro* but both parameters of toxicity and pathogenicity.

Finally, in their communication, Wylie and Korchevskiy (2021) conclude that epidemiological information is required to filling the data gaps. The aim of the FPTI model is just to deliver a predictive tool to make the global community aware of the existence of a natural hazard and its toxicity/pathogenicity potential in the attempt to avoid exposure of the population and working forces by invoking the precautionary principle, which is a well-known concept as far as asbestos minerals are concerned (see for example, Joshi and Gupta, 2004). Even without the data provided by our works, the management of the CDRP site enlighteningly applied the precautionary principle and has borne substantial costs for the dust control, demarcation of regulated areas, use of personal worker protections like respirators (Erskine and Bailey, 2018) so that hopefully there will not be epidemiological data to discuss.

The FPTI model is quite recent and obviously requires further experimental verification and confirmation in order to improve the classification of critical fibre-related parameters. In the specific case of fibrous glaucophane, it is the opinion of the authors that only by constructive comparison between the various existing models will it be possible to determine its actual potential for toxicity and carcinogenicity. Moreover, the theoretical and mathematical models and *in vitro* toxicity data should be supplemented with *in vivo* carcinogenicity data to complete the framework of predictive tools to classify the actual hazard of this mineral fibre so that proper environmental risk reduction procedures can be universally accepted.

CRediT authorship contribution statement

Alessandro F. Gualtieri: Conceptualization, Writing – review & editing. **Dario Di Giuseppe:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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