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Carcinogenicity of fibrous glaucophane: How should we fill the data gaps?

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Dear Editor,

In his recent paper published by your journal, A. Gualtieri (2021) attempted to evaluate toxicity of a fibrous glaucophane, the amphibole mineral that drew much interest because of its presence in a large construction site in California – the Calaveras Dam. Epidemiological observations on cancer among workers and/or populations exposed to glaucophane are unavailable. The author suggested that glaucophane samples contain a significant fraction of very thin fibers that should increase the carcinogenicity. Actually, Gualtieri attempted to quantify so called "fiber potential toxicity index (FPTI)" and determined that this index is equal to 2.77 for glaucophane, 2.73 for crocidolite (known as the most toxic amphibole asbestos), and 2.22 for chrysotile. The paper also referred to our recent study (Wylie et al. 2020) suggesting that "surprisingly" we found only a few (about 1%) fibrous glaucophane fibers from the Calaveras Dam of the width that "will enter the deep lung and be transported to the mesothelial surface." We believe that the audience of your journal would benefit from some clarifications on this matter.

First of all, in our work we utilized the results of B. Erskine who provided us with aerosol data collected downwind and just outside the construction area from the Calaveras Dam, including the sizing of 27,650 particles of glaucophane. Various metrics can be used to characterize the size of elongate mineral particles (EMPs) population. We demonstrated in our work that two of the consistent metrics of EMP carcinogenicity are the parameters EMPA and EMPB: EMPA is the fraction (%) of EMPs longer than 5 μm and thinner than 0.15 μm, to all EMPs longer than 5 μm; EMPB is calculated similarly, but EMPs thinner than 0.25 μm are counted. Our results are consistent with numerous previous studies. For example, Stanton et al. (1981) used statistical analysis to maximize the correlation coefficients between logit of tumor probability in rats with common logarithm of number of particles per microgram in different dimensional ranges installed in the rat pleura. He found that the highest correlation was observed between pleural sarcoma and particles longer than 8 μm and thinner than 0.25 μm. Both length and width apparently affect the carcinogenic mode of action, especially for mesothelioma development; the elongate particle should be able to penetrate deep in the lung tissue (that might be driven by the width of rigid particles), and then persist in the lungs for prolonged time, not being removed by the macrophages (that can be more probable for longer fibers), producing traumatic effects on the cells (that might be a function of chemical composition, surface charge, and other characteristics). We developed a series of mathematical models allowing prediction of the potency of amphibole particles based on their width. We limited the criteria to particles longer than 5 μm because most of the epidemiological studies for asbestos used it as a cut point for exposure measurements. The models we developed are based on the determination of the relationship between the dimensionality of EMPs and observed epidemiological data for various cohorts.

For California airborne glaucophane particles from the Calaveras Dam, the parameter EMPA was calculated as 1.2 and EMPB as 7.01%. These can be compared, for example, to Australia riebeckite (crocidolite) that has EMPA of 46.7% and EMPB of 71.1%. Based on our models, the mesothelioma potency R_M for glaucophane (as calculated by Hodgson and Darnton method, 2000) should be very low (the power law models yield R_M of 0.0085%, as an average between EMPA and EMPB estimations, vs. approximately 0.5% as estimated for different varieties of crocidolite).

It is easy to see that Calaveras Dam glaucophane contains a sizable fraction of very thin particles; however, most of them are also very short. Gualtieri (Di Giuseppe et al., 2019) mentioned that the mean length of the glaucophane particles of the investigated sample from San Anselmo, Marin County (CA, USA) is < 5 μm (the sample was taken about 115 km from the Calaveras Dam site). Our sample from the Calaveras Dam has a mean length of 6.94 μm; however, only about 54% of the particles are longer than 5 μm, which significantly changes the outlook for the carcinogenicity of the mineral.

Recently, we developed a series of models that relate mesothelioma and lung cancer toxicity of amphibole particles with both their length and width. We demonstrated, in particular, that mesothelioma potency of amphibole EMPs can be approximated as $R_M = -0.0053 + 0.00025\ \text{Median}(L^{1.19}/W^{2.97})$ and lung cancer potency as $R_L = -0.43 + 0.268\ \text{Median}(L^{0.4}/W^{1.17})$, where L –length, W - width, and Median() denotes the median taken for the different combinations of length and width in the dataset of particles. Based on these models, the mesothelial carcinogenicity of the Calaveras Dam glaucophane would be

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estimated as negative (non-existent), and the lung cancer potency as 0.36%, vs. Australia crocidolite estimations of 0.52% for mesothelioma and 4.82% for lung cancer, very close to the published estimations by Hodgson and Darnton (2000).

Also, if models developed by Korchevskiy et al. (2019) for prediction of mesothelioma potency based on chemical composition and dimensionality of various fiber types were used, the R_M for glaucophane can be estimated as 0.013–0.017%, approximately 35 times lower than for crocidolite. The estimation from the 2019 model is very close to the range of values from Wylie et al. (2020) (average of 0.0085%). It is as well noteworthy that even in this case Calaveras Dam glaucophane appears to have mesothelioma potency higher than chrysotile by a factor of 10, while Gualtieri's FPTI index for glaucophane exceeds the chrysotile index only by 25%. It is possible that in the case of San Anselmo samples, we deal with a more fibrous variety of glaucophane than in the Calaveras Dam situation. The median aspect ratio of glaucophane reported by Giuseppe et al. (2019) is 18, while the sample we described has median aspect ratio of 5.4. However, even increasing the median aspect ratio in this proportion, based on the model from Korchevskiy et al. (2019) we would still get a mesothelioma potency R_M around 0.2%, significantly lower than for crocidolite.

Also, the glaucophane from California can be assessed by another useful criteria that was developed by Wylie: the fibrosity index defined as a slope factor between log-transformed width by log-transformed length of EMPs (Wylie and Schweitzer, 1982). The coefficient is usually higher for nonasbestiform varieties of particles. For glaucophane, the fibrosity index appears to be equal to 0.77. (It can be compared, for example, with nonasbestiform cummingtonite-grunerite from Homestake gold mine in South Dakota, where the average fibrosity index was 0.81, vs. Transvaal commercial grunerite with the fibrosity index of 0.17). As with other metrics we used, the fibrosity index correlates various parameters to evaluate the characteristics of the particles; in this case, it is the relationship between length and width that has been used to see a multidimensional, and not just a flat, picture of the fibrous agents from the position of their possible toxicity.

Significant issue with the FPTI index, proposed by Gualtieri, is the lack of scaling by the observed carcinogenic potential: the index is developed from a set of parameters, which, taken separately, can be seen as predictors of toxicity. However, their combinations have not been tested for their ability to predict cancer potency in humans. For example, 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 (for log–log correlation, $R^2 = 0.682$, $P = 0.2$; for untransformed variables $R^2 = 0.003$, $P = 0.92$). It demonstrates the fact that the combination of the parameters in FPTI index has not, in reality, expressed the integral carcinogenicity of mineral particles. The example with glaucophane is very telling; the models, developed based on the epidemiological data, place this variety of amphiboles in the category of low carcinogenicity. The index of Gualtieri, however, shows glaucophane as expressing higher toxic potential than crocidolite, which was observed producing the highest mesothelioma potency among all other amphiboles. Surprisingly, Gualtieri et al. (2021) recently concluded that glaucophane, according to in vitro tests, "apparently induces lower toxic effects compared to crocidolite." Obviously, further toxicological studies, and especially epidemiological observations, would be needed to fully assess the carcinogenicity of California glaucophane. However, filling the data gaps without due consideration of epidemiological information does not seem like a good idea.

CRediT authorship contribution statement

Ann G. Wylie: methodology, Writing - review & editing. **Andrey A. Korchevskiy:** Conceptualization, Methodology, Formal analysis, Writing - original draft, 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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