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Letter to the Editor: Epidemiology holds a key to the validation of toxicological models for elongate mineral particles

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ABSTRACT

The authors reply to the comments of Drs. Gualtieri and di Giuseppe on the short communication by Wylie and Korchevskiy – Carcinogenicity of fibrous glaucophane: how to fill data gaps? (2021 Current Research in Toxicology Volume 2, pp. 202–203). The role of epidemiology in establishing the toxicity of elongate mineral particles is emphasized. The validation of quantitative structure–activity relationship (QSAR) models by disease outcome is mentioned as one of the most important tools in advancing the new approaches in mineral particle toxicology.

1. Dear Editor,

We appreciate the attention of Drs. Gualtieri and di Giuseppe to our short communication "Carcinogenicity of fibrous glaucophane: How should we fill the data gaps?"

The authors correctly stated that our results in assessing the carcinogenic potency of fibrous glaucophane were based on the airborne data vs. the bulk sample that Dr. Gualtieri analyzed in his study. It is obvious in this context that airborne samples (which included thousands of particles with available morphometry) allowed for better evaluation of possible carcinogenic potency of the full range of particle sizes in an exposure. The air samples of glaucophane that we discussed were collected just outside the construction zone of the Calaveras Dam in California, USA. We concluded that the airborne elongate mineral particles of glaucophane have typical characteristics of a cloud with significant fraction of nonasbestiform particles. It should be noted that data collected by D. Hernandez (reported in Wylie et al., 2020) within the Calavaras Dam construction zone indicated comparatively higher fraction of long narrow (length $>$ 5 μm, width $\leq$ 0.15 μm) glaucophane particles over the exposure outside the project boundaries; however, the fraction of long, thin fibers was still significantly lower than for asbestiform riebeckite (crocidolite asbestos). This fact serves as a valid argument for our suggestion that the carcinogenic potency of fibrous glaucophane is quantifiable and sizably lower than for crocidolite with its prevailing asbestiform habit, based on quantitative structure–activity relationships (QSAR) models developed over the last several years (Korchevskiy et al., 2019; Wylie et al., 2020; Korchevskiy and Wylie, 2021). It should be noted that the difference in carcinogenic potency of asbestiform and nonasbestiform particles was convincingly demonstrated in laboratory testing (like in Mossman, 2008), as well as in epidemiological studies (Gamble and Gibbs, 2008).

From the comments of Drs. Gualtieri and di Giuseppe, it remains unclear how to interpret the fact that the estimation of a Fibre Potential Toxicity/Pathogenicity Index (FPTI) developed by their team yields a value for glaucophane compared to or exceeding the toxicity/-pathogenicity level for crocidolite, the most carcinogenic commercial type of amphiboles (Hodgson and Darnton, 2000; Berman and Crump, 2008; Garabrant and Pastula, 2018). In addition, the FTPI index values do not correlate with published mesothelioma potency for the major mineral types of asbestos nor does the index correlates with the published potency factors for lung carcinoma derived from occupational cohorts' information (Hodgson and Darnton, 2000; Berman and Crump, 2008).

In recognition of this problem, Drs. Gualtieri and di Giuseppe explain these differences by pointing out that "the fibres investigated in our work are not the same as those to which the workers were exposed." The variability in toxicity in a single mineral from two nearby sources is certainly possible since habit can vary over a short distance. This reminds us that great care must be taken in associating toxicity with the location of the occurrence and a description of the habit, not just the mineral name.

However, toxicological modelling and risk assessment can be applied to specific cohorts of workers and communities if correct expo-

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sure characteristics and validated models are utilized. In particular, the approach proposed by our group includes the analysis of mineral particles, typical for workers' exposure, and development of the models that can be validated by epidemiological data, and then used for prediction of health outcomes of other types of exposure. In this case, epidemiological information serves as "training" set for the QSAR modelling, and predictions can be made for the "test" sets of particles without available human health data. Different methods can be used to mathematically analyse the validity of the models; for example, we utilized "leave-one-out" method to cross-validate the regression models proposed for prediction of mesothelioma and lung cancer potency factors by exclusion various data points and estimation the stability of the proposed coefficients (Cheng et al., 2017).

Dr. Gualtieri and his team apparently rejected the need to calibrate the FTPI by correlating it with the observable health effects in humans that would serve as "training" set for his index. The authors suggested that "the only quantitative methods universally accepted to date to determine the carcinogenicity of substances including mineral fibres are the *in vivo* animal testing." This statement, unfortunately, is not true for elongate mineral particles like asbestos, and for such an important health target as mesothelioma. For example, Saffiotti (2005) discussed numerous agents causing mesotheliomas in laboratory animals, while in humans the mesothelioma is seen as prevailingly related to fibrous minerals exposure. Berman and Crump (2003) addressed the differences in observations on asbestos carcinogenicity between animals and humans suggesting that it may be "due at least in part to the limited lifetime of the rat relative to the biodurability of the asbestos fiber types" or that "different mechanisms drive the effects observed in the animal studies than those that dominate for asbestos-induced cancers in humans and that such mechanisms depend more strongly on mineralogy."

Virtually all quantitative estimations of asbestos potency factors in the last several decades were prepared based on the epidemiological data, and not on attempts to extrapolate in vitro or *in vivo* tests results to human populations (see, for example, the history of regulatory reviews for various mineral types of asbestos: US EPA, 1986; US EPA, 2017; US EPA, 2020; European Chemical Agency (ECHA), 2021). The future of toxicology in general, and asbestos toxicology in particular, lays in the utilization of available epidemiological information to develop predictive *in silico* models that would be able to involve all available mineralogical, chemical, and biological data, but can be validated only on the human health information, even if epidemiological studies on asbestos were historically limited in scope. The index of Dr. Gualtieri, however, appears to be purely empirical and not tested directly on any data that would reflect specific biological endpoints, in humans, or in laboratory animals. The toxic effects, however, cannot be considered as a simple linear combination of parameters, even if each parameter reflects some measurable response of the organism on some level of the biological system.

It should be noted that Dr. Gualtieri's team has collected valuable information on *in vivo* and *in vitro* effects, as well as chemical and physical characteristics of various mineral types of elongate particles. Combining this information with available epidemiological data would help to develop new models allowing determination of which measurable parameters are predictive for specific health outcomes, separately for carcinogenic effects (like mesothelioma and lung carcinoma) and non-cancerous pathological conditions (like pleural plaques and asbestosis), related to fibrous agents. However, without this type of correlation with human epidemiological observations, any toxicity index or QSAR model cannot be considered as relevant for protecting health of workers and communities.

CRediT authorship contribution statement

Ann Wylie: Conceptualization, Writing – review & editing. **Andrey Korchevskiy:** Conceptualization, 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.

References

Berman, D.W., Crump, K.S., 2003. Final Draft: Technical support document for a protocol to assess asbestos-related risk. EPA #9345.4-06. Document Display | NEPIS | US EPA.

Berman, D.W., Crump, K.S., 2008. Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit. Rev. Toxicol. 38 (Suppl 1), 1–47. https://doi.org/10.1080/10408440802276167.

Cheng, H., Garrick, D., Fernando, R., 2017. Efficient strategies for leave-one-out cross validation for genomic best linear unbiased prediction. J. Anim. Sci. Biotechnol. 8, 38. https://doi.org/10.1186/s40104-017-0164-6.

European Chemical Agency (ECHA), 2021. ECHA Scientific report for evaluation of limit values for asbestos at the workplace. 4605fc92-18a2-ae48-f977-4dffdecfec11 (europa.eu).

Gamble, J.F., Gibbs, G.W., 2008. An evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. Regul. Toxicol. Pharmacol. 52 (1 Suppl), S154–186. https://doi.org/10.1016/j.yrtph.2007.09.020. Epub 2007 Oct 22 PMID: 18396365.

Garabrant, D.H., Pastula, S.T., 2018. A comparison of asbestos fiber potency and elongate mineral particle (EMP) potency for mesothelioma in humans. Toxicol. Appl. Pharmacol. 361, 127–136. https://doi.org/10.1016/j.taap.2018.07.003. Epub 2018 Aug 2 PMID: 30077661.

Hodgson, J., Darnton, A., 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann. Occup. Hygiene 44 (8), 565–601 https://pubmed.ncbi.nlm.nih.gov/11108782/.

Korchevskiy, A., Rasmuson, J., Rasmuson, E., 2019. Empirical model of mesothelioma potency factors for different mineral fibers based on their chemical composition and dimensionality. Inhal. Toxicol. 31 (5), 180–191. https://doi.org/10.1080/08958378.2019.1640320. Epub 2019 Jul 22.

Korchevskiy, A.A., Wylie, A.G., 2021. Dimensional determinants for the carcinogenic potency of elongate amphibole particles. Inhal. Toxicol. 33 (6–8), 244–259. https://doi.org/10.1080/08958378.2021.1971340.

Mossman, B.T., 2008. Assessment of the pathogenic potential of asbestiform vs. non-asbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. Regul. Toxicol. Pharmacol. 52 (1 Supp), S200–203. https://doi.org/10.1016/j.yrtph.2007.10.004.

Saffiotti, U., 2005. Mesothelioma carcinogenesis:in vivo models. In: Pass, H.I., Vogelzang, N.J., Carbone, M., editors. Malignant Mesothelioma: advances in pathogenesis, diagnosis, and translational therapies. New York, NY, Springer, p. 605. ISBN:0387229493.

Epa, U.S., 1986. Airborne Asbestos Health Assessment Update.

U.S. EPA, 2017. Toxicological review of Libby amphibole asbestos. EPA/635/R-11/002F.

U.S. EPA, 2020. Risk evaluation for asbestos. Past I. Chrysotile asbestos. EPA-740-R1-8012.

Wylie, A.G., Korchevskiy, A., Segrave, A.M., Duane, A., 2020. Modeling mesothelioma risk factors from amphibole fiber dimensionality: mineralogical and epidemiological perspective. J. Appl. Toxicol. 40 (4), 515–524. https://doi.org/10.1002/jat.3923.