Correspondence regarding the article "The asbestos fibre burden in human lungs: new insights into the chrysotile debate"

To the Editor:

The article by Feder *et al.* [1] states that the lung asbestos fibre burden in 23 955 patients was analysed to address fibre type and biopersistence; data from 12 patients undergoing two tissue excisions at intervals at least 4 years were considered.

We believe that the article has serious shortcomings, as follows.

1) Unclear aim. Contrary to the authors' claim, there is no ongoing debate about the biopersistence of chrysotile asbestos among independent, credible scientists. In support of their claim that such a debate exists, the authors rely on an article commissioned, funded and developed in collaboration with asbestos lobbyists.

2) Faulty study design. Significant scientific problems in patient/sample selection and applied methods exist. First, the small sample size: only 12 (0.05%) of the 23 955 cases were analysed with two investigations; only six had electron microscopic examination of tissue. Second, the selection criterion of 500 asbestos bodies per gramme of wet lung is discretionary and arbitrary. Third, relationships between outcome and fibre-years were not examined using a detailed occupational history. No statistical analysis accounting for occupation/exposures, interim exposures and latency periods, and exposure changes over recent decades is reported.

3) Methods. The authors do not explain why they used both field energy (FE) scanning electron microscopy (SEM) and transmission electron microscopy (TEM), nor is it clear which data come from which method in the supplementary table. TEM is regarded as the method of choice by impartial and credible pathologists; the limitations of SEM have been discussed previously [2].

The use of FE-SEM and TEM on autopsy specimens alone does not allow the authors to say anything about the change in the number of chrysotile fibres over time.

The term "pulmonary asbestos fibre concentration" defined as "total of asbestos bodies and bare fibres" is incorrectly conflated with asbestos fibre concentration or burden as generally understood.

4) Results. First, there is no information on fibre length, which would be crucial for understanding outcome since short fibres are more rapidly cleared from the lung [3, 4].

Second, in the six cases analysed with electron microscopy, the fibre counts reported are generally similar to, or even lower than, asbestos body counts. This unusual finding contradicts the literature where total fibres outnumber asbestos bodies by three orders of magnitude [5].

Third, in a large number of ferruginous bodies, the authors were unable to identify the core material. How did the authors define a ferruginous body as asbestos and non-asbestos in those cases not subjected to electron microscopy?

Last, the authors mention that "asbestos grading followed national and international criteria, *i.e.* primarily the Helsinki criteria". It is unclear which criteria were used in each case. There are significant differences

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All asbestos types cause asbestosis (cancer): chrysotile is not biopersistent, so fibre analysis is not diagnostic http://ow.ly/BOLC30grqYg

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between the NIOSH/CAP definition and the definition of Roggli and co-workers and its respective formulation in the Helsinki criteria 2014 [6] (for further details, see [7]).

5) Data analysis, data interpretation and conclusions. First, in the six cases with fibre type differentiation, 10% to 95% were reported to represent chrysotile. In Germany, about 94% of asbestos used was chrysotile. The relative paucity of chrysotile fibres in cases 1 and 2 (33% of the cases) with intervals of 14 and 21 years between the first and second examinations is consistent with low biopersistence of chrysotile fibres.

Second, the authors state "Thus fibre clearance and biopersistence are considered the most important factors for diagnostics and risk assessment of malignant and non-malignant diseases." In fact, diagnosis is based mainly on a thorough occupational history and noninvasive clinical findings; risk assessment is related to fibre concentration in the workplace [8].

Third, the major interpretation of the data by the authors is that chrysotile fibre counts, like those of amphibole fibres, do not change over time in the human lung. Their findings and extensive literature show just the opposite [8].

6) Discussion. The authors claim an ongoing debate about the hazardous nature of chrysotile. Publications not cited by Feder *et al.* [1] (IARC, WHO), and other professional bodies and government agencies contradict this claim, concluding that chrysotile asbestos exposure increases risk for asbestosis, mesothelioma, lung and other cancers [9].

7) Medico-legal relevance. There is grave risk that the publication by Feder *et al.* [1] will influence outcomes in the adjudication of asbestos-related disease in the legal system and that, as a result, the injured worker will suffer unfairly and unjustly. This risk would apply to those with a history of occupational exposure to chrysotile asbestos and in whom few or no asbestos fibres are found in the lung years later. The claim by Feder *et al.* [1] that chrysotile fibres are biopersistent in the lung could be used in courts of law to deny justice to asbestos-harmed victims.

8) Conflicts of interest. The authors fail to disclose significant financial conflicting interests [10].

In conclusion, Feder *et al.* [1] provide misleading findings that fail to refute the generally accepted tenet that chrysotile asbestos fibres are not biopersistent in the human lung. Neither their clinical nor their statistical analyses, nor the literature, support their claims.

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To the Editor:

We read with interest the generally excellent article by Feder *et al.* [1] published in the *European Respiratory Journal* and we would like to add just a comment. Authors screened the German Mesothelioma Register for patients with asbestos body (AB) counts ⩾500 per gramme of wet lung (corresponding to approximately ⩾5000 AB per gramme of dry lung tissue) which had been analysed twice from different tissue excisions at minimum interval of 4 years. In the 12 patients with longitudinal data the asbestos fibre burden in the lung tissue was stable in particular for chrysotile. Authors stated that the study was the first to present intra-individual longitudinal data about the asbestos fibre burden in living human lungs.

The measure of the fibre load of lung tissue using electron microscopy represents the best indicator of retained dose, but this can only be performed after open lung biopsy, lung surgery or death. Mineralogical analysis of bronchoalveolar lavage fluid (BALF) by electron microscopy has been successfully used as a marker of asbestos fibre load in a number of studies [2–6]. Its use to characterise asbestos lung burden is generally accepted [7, 8]. In 2007 we published a study whose purpose was to assess the reliability of asbestos fibre concentration in BALF as a marker of past asbestos exposure by carrying out at different times the mineralogical analysis of BALF in the same patient and comparing the results [9]. Mineralogical analysis of BALF was carried out in 22 patients who underwent diagnostic fibreoptic bronchoscopy twice (the first to assess the past asbestos exposure, the second for different clinical reasons). The mean lag time between the first and the second bronchoalveolar lavage was 4.0±2.3 years (median 4, range 1–10 years). In 16 patients (72.7%), a reduction of concentration in BALF of both chrysotile and amphiboles was observed, but the differences were not statistically significant while a significant decrease in AB concentration between the first and the second bronchoalveolar lavage was found.

Although the article of Feder *et al.* [1] is not really the first to consider longitudinal individual data, it is of a great interest because it confirms histologically in the lung tissue what has been previously observed in the BALF. Moreover in this case the lag time from the cessation of exposure was much greater. The nonsignificant reduction of chrysotile and amphiboles fibres between the first and the second bronchoalveolar lavage observed in many cases was not apparently attributable to the pulmonary clearance because it was not related to the lag time between the first and the second BAL. Maybe it could be partially explained by the effect of the first lavage when the second was performed in the same lung region. Workers who have been exposed for a long time have concentrations of fibres in BALF which are higher than subjects who have been more recently exposed [4, 5]. Even if this information leads back to the high exposure in the past, it confirms the biopersistence of asbestos fibres in the human lung, in agreement with the results of Feder *et al.* [1]. We agree with the authors that the sustained presence of both chrysotile and amphibole fibres causes lung diseases even many years after exposure cessation. This could also cause a different latency of asbestos-related lung cancer in comparison to those related to smoking.

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From the authors:

We appreciate the opportunity to respond to the correspondence from X. Baur and colleagues regarding our article recently published in the *European Respiratory Journal* [1].

We added the subtitle "new insights into the chrysotile debate" to the title of our manuscript. In their accompanying editorial, Nemery *et al.* [2] asked about the nature of the debate and stated among others that the term "chrysotile debate is not neutral". The correspondence from X. Baur and colleagues corroborates this view. It demonstrates that there is indeed a heavy debate, mainly going on in Germany, but, as suggested by the large number of authors of this correspondence, it is also relevant in an international frame. Of note, people who have fought for the global ban of asbestos were co-authors of the article.

In our view, "debates" and discussions about scientific topics are common and needed. Multiple debates about chrysotile exist with changing aspects over time. The debate about the hazard of chrysotile inducing malignant and non-malignant pleural and lung diseases is over. Still open is the question about biopersistence of chrysotile in the lungs of affected workers.

In contrast to animal data [3], our manuscript shows high biopersistence of chrysotile fibres in human lungs [1], a result that perfectly fits to the well-known characteristics of asbestos: "imperishable", "rot-proof", "extremely resistant". Our data explain the toxicity of the fibre and are a strong argument for a global ban of asbestos.

So what is the motivation of the authors of the correspondence? They fear that our findings may influence compensation claims. It was clearly the aim of our study to assess biopersistence of asbestos fibres, irrespective of any socio-economic implications which may even differ between countries. It is our experience that cases with relevant occupational asbestos exposure and a clinical picture of idiopathic pulmonary fibrosis without histological evidence of asbestosis are extremely rare. It is an international consensus; if one considers the Helsinki criteria as a clinical guideline, it should be clear that the histological diagnosis of asbestosis requires the existence of fibrosis *plus* the demonstration of asbestos

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bodies or uncoated asbestos fibres [4]. According to this consensus, asbestosis with few or no detectable asbestos fibres is speculative. Indeed, our manuscript makes the existence of such rare cases even more speculative. It should be noted that there are much higher numbers of patients with lung "fibrosis" who are diagnosed to have asbestosis by histology [5, 6]. Those patients are then recommended for compensation. Thus we do not see any disadvantages for patients with true asbestosis.

The criticism raised in the correspondence from X. Baur and colleagues is manifold and we cannot give a point to point reply within the space limit of the journal. Concerning methodological problems we refer to our method section and a more detailed view on some of the controversies published recently [7]. Here we would like to comment on the major points raised.

Regarding study design and the allegedly low number of subjects we are strongly convinced that this is not a real weakness of our study. As outlined in our manuscript, such data are difficult to obtain and therefore unique. It is a longitudinal observational study which is largely unaffected by the sample size. This was also recognised by Nemery *et al.* [2] in their editorial where they concluded that "…it is not unreasonable to assume that similar results would probably be obtained in a study with more patients". To support their conclusion, Nemery *et al.* [2] added valuable information about seven patients who underwent repetitive bronchoalveolar lavage. This supplementary analysis confirms our data. There is an additional study by Sartorelli *et al.* [8] of a further 22 patients, who too obtained similar results from repeated bronchoalveolar lavage fluid samples.

Concerning the chrysotile to amphibole ratio it is well known that the chrysotile fraction in the human lung is lower than at workplaces [9–12], as mentioned in our manuscript. This does not allow any statement about biopersistence of chrysotile in human lungs. It just is an observation, that chrysotile is deposited and accumulated in human lungs to a lower degree than amphibole. This is generally accepted and not challenged by our data.

Our data demonstrate that this accumulated asbestos fibre burden in the human lung is stable after exposure cessation and that this is true also for chrysotile. This was not known before as no one so far had analysed longitudinal intra-individual data from human lung tissue. As an explanation we discussed that the failure of chrysotile to accumulate in human lungs reflects events that occur early after exposure rather than long-term clearance mechanisms, as postulated by others earlier [13]. Thus our findings are not the opposite of but consistent with extensive literature [14].

The correspondence claims undisclosed financial conflicts of interest. We are convinced that putative conflicts of interest were disclosed properly as requested by the *European Respiratory Journal*.

In conclusion, we have shown for the first time that asbestos fibres including chrysotile are highly biopersistent in human lungs. We see these findings *per se* worth reporting.

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