Thieme

Only One Lesson to be Learned

Reply to X. Baur: Pneumologie 2016; 70: 405–412

Although we agree that the high numbers of diseases caused by asbestos worldwide and the consequences for individual patients merit the word "tragedy", we wish to comment a few issues which represent the repeatedly [1–3] published opinions of Prof. Baur, but are not common scientific knowledge.

Asbestos bodies and fiber concentrations in lung tissue – general aspects

The pathologic diagnosis of asbestosis is never made from the result of a lung dust fiber analysis alone – as Prof. Baur tries to suggest –, instead it is a combination of the result of the asbestos fiber burden of the lung and the histopathologic findings – and sometimes of the histology alone. The 1997 Helsinki criteria [4] state the following: "*A histological diagnosis of asbestosis requires the identification of diffuse interstitial fibrosis in well inflated lung tissue remote from a lung cancer or other mass lesion, plus the presence of either 2 or more asbestos bodies in tissue with a section area of 1 cm^2 or a count of uncoated asbestos fibers that falls into the range recorded for asbestosis by the same laboratory*".

We interpret this statement as an agreement within an international expert group. Beyond this statement there is no cut-off value for the fiber burden in the lung for the diagnosis of asbestosis. To postulate that at least 1000 asbestos bodies/cm^3 would be needed for diagnosis of asbestosis is simply not true. If such statements were made earlier this was in contrast to scientific knowledge, not covered by any agreement, and never practiced by the German Mesothelioma Register.

It is extremely rare that the diagnosis of nonmalignant respiratory diseases due to asbestos is based on pathological examinations (our estimate is below 3 percent). In contrast, if a diagnosis of lung cancer is made, pathological examinations of lung tissue of cases with no radiological evidence of asbestos exposure and asbestos exposure estimates below 25 fiber-years (about 20 percent of all cases) result in about additional 10 percent of occupational diseases due to the diagnosis of minimal asbestosis [5].

Parallel developments in Professor Roggli's private institute at Duke University Medical Center, NC, USA

It is a frequent tactic to discredit persons if there are no arguments. We agree that asbestos industry tried to put forward the hypothesis that chrysotile does not cause fibrosis and cancer. As outlined below, there is good evidence to consider chrysotile asbestos as potent as amphiboles for the causation of lung fibrosis and cancer. The 1997 Helsinki criteria state the following: "*In order to achieve reasonable comparability between different studies, a standardized system for the histological diagnosis and grading of asbestosis is required. The Roggli-Pratt modification of the CAP-NIOSH system is recommended as a reasonably simple and reproducible scheme for this purpose.*" The Roggli-Pratt modification does not consider fibrosis of the bronchiolar walls alone as minimal asbestosis [6]. It is our experience that isolated bronchiolar fibrosis is histologically an extremely rare finding, as the histologic tissue slide is a 2-dimensional picture of a 3-dimensional organ. Because of the contiguity of the bronchioli respiratorii to the alveolar wall a fibrosis of the bronchioli respiratorii always also affects the adjacent alveolar walls and consequently would lead to a diagnosis of asbestosis grade 1. If more than the first layer of adjacent alveolar walls is affected it is a grade 2 asbestosis. Thus it should be of minor importance if the CAP-NIOSH definition or the Roggli-Pratt modification is used.

Asbestosis with few or even missing asbestos bodies and asbestos fibers in lung tissue and the chrysotile "hit-and run phenomenon"

The *hit and run phenomenon* (German: Fahrerfluchtphänomen) – although unknown in the international medical literature – is Prof. Baur's key argument against the usefulness of fiber analyses in the diagnosis of asbestos-induced diseases. This argument sounds plausible: it is well known that chrysotile fibers, which were used predominantly in Germany, are much more soluble and show short half-lifes in animal experiments. Thus it should be obvious that these fibers should not be found in human lung tissue many years after exposure cessation. This hypothesis ignores that asbestos fibers are actually detected in human lung tissue and bronchoalveolar lavage fluid many years after exposure cessation [7–11]. This is true also for chrysotile fibers, which show compartimentalization [7, 9]. These findings are not new: "… studies indicate that, although both amphibole and chrysotile asbestos fibers are found in the lungs of the general population and exposed workers, amphibole fibers are universally present in disproportionately large and chrysotile fibers in disproportionately small amounts compared to their known abundance in the original inhaled dusts" [7]. Thus chrysotile is somewhat less biopersistent than amphiboles, it is however not completely eliminated from the human lung. These data are corroborated by the findings of the Mesothelioma Register [5]. More than two decades after the asbestos ban in Germany high counts of asbestos bodies and uncoated fibers including chrysotile are detected by light and electron microscopy and high numbers of patients are diagnosed with asbestos-induced lung diseases according to the Helsinki criteria.

The existence of a *hit and run phenomenon* would be of high importance not only for diagnosis, but also for risk assess-

ment. There is an overwhelming body of scientific evidence, that besides dose and dimension, durability (biopersistence) is the major determinant of fiber toxicity [12]. To suggest that chrysotile has low biopersistence in human lung tissue would give an argument to the asbestos industry that chrysotile exposure is without risk, a view that is not shared by us and – to our knowledge – not by any national or international organization that is engaged in risk assessment of asbestos fibers.

Inadmissible equation of the pathological-histological findings of UIP (usual interstitial pneumonia) with IPF (idiopathic pulmonary fibrosis)

If the author wants to point to similarities between histological findings of IPF and asbestosis, we fully agree. Some years ago, a group of pathologists stated the following differences between asbestosis and IPF: *"First, the interstitial fibrosis of asbestosis is accompanied by very little inflammation, which, although not marked, is better developed in idiopathic pulmonary fibrosis. Second, in keeping with the slow tempo of the disease, the fibroblastic foci that characterize idiopathic pulmonary fibrosis are infrequent in asbestosis. Third, asbestosis is almost always accompanied by mild fibrosis of the visceral pleura, a feature that is rare in idiopathic pulmonary fibrosis"* [6]. This is also the experience of the Mesothelioma Register.

Epidemiologically, a close association between mesothelioma and IPF mortality has been reported, and also asbestos imports to the UK were associated with IPF mortality [13], but a recent pathological study stated that UIP pattern fibrosis in exposed cohorts is extremely rare. This study concluded that UIP pattern fibrosis should not be regarded as genuine asbestosis [14]. It is our understanding that the differential diagnosis between asbestosis and IPF remains a diagnostic challenge with a high risk of pitfalls to distinguish both diseases, especially without fiber analysis.

Asbestosis versus IPF: Inadmissible elimination diagnostics exclusively on the basis of collected pathological-histological findings and fiber analyses

This paragraph repeats the criticism of fiber analyses per se and is discussed elsewhere in this manuscript. If the author states that not a single scientific article has shown that the inability to detect fibers excludes asbestosis we wonder what design such a study would have. In the absence of an accepted gold standard for asbestosis it should be impossible to answer this question. So far an accepted gold-standard for asbestosis is the histologic diagnosis of lung fibrosis with incorporated asbestos bodies – alternatively the histologic diagnosis of lung fibrosis together with an asbestos fiber burden of the lung determined by electron microscopy.

Further aspects of the findings in the lungs of asbestos-exposed persons and the limitations of the pathological-histological diagnostics

Prof. Baur states that there is agreement that asbestos bodies hold no pathogenetic significance. We wonder how he comes to such a conclusion (there is no reference). Historically asbestosis was first described at the beginning of the last century by pathologists who detected asbestos bodies in the lungs of workers with lung fibrosis [15 – 17]. Pathologists, and not epidemiologists, concluded at that time that asbestos is a hazard for human health. Asbestosis was defined as an occupational disease by German authorities as a consequence of these pathological findings. We consider it weird to postulate nowadays that the diagnosis of asbestosis should be made without pathologists.

Epidemiological-statistical associations

In this paragraph the author addresses several points:

1. The author claims that epidemiological studies show that asbestos is a risk factor for ovarian cancer, gastrointestinal cancers and COPD. It is not our intention to comment on these epidemiologic studies. For compensation purposes it is one point to establish an association between a specific cause and a disease, i. e. to define a hazard, but it is also important to define exposure degrees which allow a decision. Thus we think that German authorities (Sachverständigenbeirat des BMAS) have to decide whether rare diseases will appear in the list of occupational diseases and define the requirements for compensation. It is our understanding that it is important to support this committee. For COPD, which is not a rare disease, there is a mention in the AWMF guideline [18]. It is a complex paragraph, which points to the occurrence of airway obstruction in asbestosis, but we see no mention that asbestos causes COPD. It is our understanding that asbestos exposure usually occurred almost exclusively at workplaces with complex and high co-exposures to particles. Thus it is not a surprise that epidemiological studies find negative effects on lung function in these cohorts. Co-exposures were not examined in a review performed by the author concerning this topic [19].
2. The author states that newer review articles negate adverse effects of chrysotile. It is an old debate whether chrysotile is less potent than amphiboles. In accordance with German authorities and the MAK commission we believe that there is good evidence that chrysotile causes fibrosis and cancer. Concerning the dose-response relationship chrysotile and amphiboles are considered of similar potency, although this is less clear.
3. The author states that a recent manuscript which says that asbestos exposure in the distant past is more important than subsequent exposures for mesothelioma is wrong and the authors have a conflict of interest. This point has no importance in Germany, where latency or the dose-response relationship are not considered for mesothelioma.
4. The author states that the number of subjects with asbestosis is high in those with exposure to asbestos, whereas the number subjects with IPF is much lower in the general population. We cannot understand the rationale of this argument, but – as discussed above – we are concerned

about misclassification of IPF and asbestosis, as both diseases share both histological and radiological similarities – but also differences, mainly the incorporated asbestos fibers [6, 14, 20, 21].

Dose-response-relation in asbestos-caused lung cancer

German authorities have published a dose-response relationship for asbestos [22]. This dose-response relationship was set up for preventive purposes of lung cancer, but not for compensation. The calculation was based on the US-EPA unit risk with a risk of approximately 0.1 % per F/mL years. Due to heterogeneity of the available epidemiological studies the committee made several assumptions, among them that chrysotile and amphiboles are equally potent, that the dose-response is linear and that a correction for the method of fiber counting is not considered. This statement is in accordance with the 1997 Helsinki consensus statement and we cannot see any data torturing.

Significance of the medical occupational history and technical inspectorate (occupational hygienist) evaluations of exposure frequently not performed or considered

We see limitations of fiber analyses as well as occupational history for the assessment of past asbestos exposure. Some years ago, Prof. Nemery's group commented on that subject [23]: *"Why do we not agree that the past work history should be the gold standard for past asbestos exposure? The history is rarely, if ever, an accurate reflection of the level of exposure, particularly if this is obtained by questioning the patient, which is often the only available option. People sometimes ignore totally that they have ever been exposed to asbestos, either at work, or elsewhere; in addition, when they do know that they have worked with asbestos-containing materials, most are not capable of indicating how high their exposure has been. Clinical experience and a large body of published evidence teaches us that substantial asbestos exposure may remain "occult," even after extensive questioning of the patient. On the other hand, some patients claim, or fear, that they have been exposed to huge quantities of asbestos, although their exposure has only been trivial. Consequently, while we agree that a detailed occupational history is an essential cornerstone in the diagnosis of asbestos-related lung disease, we do not think that it can ever be the best indicator, let alone a gold standard. … … quantitative assessments of fiber burden in lung tissue, and to some extent also in bronchoalveolar lavage, are generally more accurate indicators, although they too are not perfect, particularly to assess remote exposures to chrysotile. So, there is probably no gold standard to evaluate the degree of the past exposure to asbestos, and we are left with having to use combined approaches, including, of course, the occupational history."*

We fully agree with this statement. We want to add that the exposure degree is important for lung cancer, where a certain dose is one of several diagnostic criteria, but also for lung fibrosis quantitative exposure estimates are of some importance. However, there are further points which may help to distinguish between IPF and asbestosis, as asbestosis is often accompanied by the occurrence of pleural plaques and a longer time course of the disease. Thus fiber analyses, histology, occupational history, radiology and clinical data help to make the diagnosis.

Conclusion

Repetitive publications of Prof. Baur and others [24] suggest that prevention and compensation of asbestos-induced diseases are counteracted by collaboration of asbestos industry, scientists with conflicts of interests, the German Social Accident Insurance and the Mesothelioma Register. While prevention issues are of less importance in Germany due to the asbestos ban, his media skills help to communicate to patients and lawyers that doctors make wrong diagnoses and betray patients with intent. We consider it not ethical to unsettle patients, especially those with severe diseases as lung cancer or IPF. Thus the only lesson to be learned is that patients should continue to have confidence in their doctors and the German compensation system.

Conflicts of interests

Rolf Merget is performing medical opinions for accident insurances and courts. He is employed at the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), which is an Institute of the Ruhr University of Bochum. Andrea Tannapfel is performing pathological expertises for accident insurances and courts. She is head of the Institute of Pathology, which is an Institute of the Ruhr University of Bochum and of the German Mesothelioma Register. The latter gets third-party funds from the German Social Accident Insurance. Inke Feder is a coworker of Andrea Tannapfel and has no further conflicts of interest.

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