Int. J. Ion Mobil. Spec. (2014) 17:87–94
DOI 10.1007/s12127-014-0147-7

ORIGINAL RESEARCH

# Signals in asbestos related diseases in human breath - preliminary results

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Received: 10 December 2013 / Revised: 1 February 2014 / Accepted: 4 February 2014 / Published online: 22 February 2014


**Abstract** Several diseases occur due to asbestos exposure. Until today, asbestos predicted mortality and morbidity will increase because of the long latency period. Actually, the methods to investigate asbestos related disease are mostly invasive. Therefore, the aim of the present paper was to investigate, whether signals in human breath could be correlated to Asbestos related lung diseases using a multi-capillary column (MCC) connected to an ion mobility spectrometer (IMS) as non-invasive method. Here, the breath samples of 10 mL of 25 patients suffering from asbestos related diseases. This group includes patients with asbestos related pleural thickening with and without pulmonary fibrosis. Twelve healthy persons constitute the control group and the breath samples are compared with those of the BK4103 patients. In total 83 peaks are found in the IMS-Chromatogram. A discrimination was possible with $p$-values <0.001 for two peaks (99.9 %), <0.01 (99 %) for 5 peaks and <0.05 (95 %) for 17 peaks. The most discrimination peaks alpha pinene and 4-ethyltoluol were identified among some others with lower p-values. The corresponding Box-and-Whisker-Plots comparing both groups are presented. In addition, a decision tree including all peaks was created that shows a differentiation with alpha pinene between BK4103 (pleural plaques group) and the control group. In addition, the sensitivity was calculated to 96 %, specificity was 50 %, positive and negative predictive values were 80 % and 86 %. Ion mobility spectrometry was introduced as non-invasive method to separate both groups Asbestos related and healthy. Naturally, the findings need further confirmation on larger population groups, but encourage further investigations, too.

**Keywords** Asbestos · Pulmonary fibrosis · Breath gas analysis · MCC/IMS · Pleural thickening

## Introduction

Asbestosis is an interstitial pulmonary fibrosis with a disseminated distribution pattern, with a predominance of the lower zones caused by inhalation of asbestos fibres. Exposure to asbestos fibres also might lead to pleura thickening, pleural effusion and rounded atelectasis as well as malignant diseases [1–7].

Recently, a general review was published by Chapman et al. [8] with respect to a review of the literature and potential future applications. Therefore, the major aspects are summarized only briefly. The diseases investigated in this study are recognized as occupational disease in Germany (BK 4103, asbestosis and asbestos related diseases of the pleura).. The diagnostic procedure includes a comprehensive occupational history, clinical examinations, pulmonary function tests and imaging techniques. Details are described elsewhere [9].

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The relation to oxidative stress and inflammatory pathways induced by asbestos was discussed by Chow [10] in detail. Especially relations to pathological mechanisms are considered. Because of chronic inflammatory mechanisms in asbestos related diseases, exhaled volatile organic compounds (VOC) are of highly interest.

The aim of this paper is to find out whether signals in breath samples of patients suffering from benign asbestos related diseases are different from healthy persons. Therefore in the present paper the breath gas analysis was investigated by using an ion mobility spectrometer. Generally, several methods are under investigation to monitor the concentration of analytes in exhaled breath. For example, mass spectrometry with emphasis on proton transfer reaction mass spectrometry [11–15], ion-molecule reaction mass spectrometry [16, 17], electronic noses [18–20] or GC/MS [21–23] have been described. The detection of trace gas amounts in exhaled air using ion mobility spectrometry coupled to multi-capillary (MCC) columns was shown most recently, e.g. for Propofol [24–27] Further details with respect to the advantages and disadvantages of MCC and the IMS are described elsewhere [28–42].

## Study group

The study was approved by the ethics committee of the Knappschafts-Hospital and all subjects gave their written informed consent to participate in the pilot study.

In total 25 male patients with either asbestosis and/or asbestos related pleural thickening (BK 4103) were examined [9]. Mean age of 73 years (Range 55–84 years).

The diagnosis was carried out by a group of experts in the field of pneumoconiosis, consisting of radiologists, pulmonologists and occupational health physicians.

The diagnostic criteria were: confirmed asbestos exposure, sufficient latency between asbestos exposure and diagnosis, typical findings in the high resolution computer tomogram (HRCT) of fibrosis (excluding fibrosis changes other origin), pleural thickening detected by a specialized radiologist with application of the ICOERD-Classification [43–50]. The characteristics of the HRCT findings, the pulmonary function tests including diffusion capacity test and blood gas analysis are listed in the Tables 1 and 2. Inclusion criteria were a 2 h sobriety before taking breath sample, rule out a florid respiratory infection were asked by a questionnaire after cough or sputum. Other respiratory diseases were not an exclusion criteria.

The 12 control patients with a mean age of 36 years (Range 26–52 years) had no diagnosed diseases especially no respiratory diseases as asked in the questionnaire, were non smokers, had normal spirometric parameters and no medication. It should be noted, that the age intervals between both groups fits not perfect.

**Table 1** Patients HRCT findings

| Patient number | Profusion degree Grade 0–18 | Lung fibrosis | Pleural thickening Grade 0–3 |
|---|---|---|---|
| 1 | 0 | No | 2 |
| 2 | 3 | Yes | 2 |
| 3 | 4 | Yes | 1 |
| 4 | 10 | Yes | 2 |
| 5 | 2 | No | 1 |
| 6 | 0 | No | 3 |
| 7 | 4 | No | 3 |
| 8 | 4 | Yes | 3 |
| 9 | 0 | No | 3 |
| 10 | 4 | Yes | 3 |
| 11 | 0 | No | 1 |
| 12 | 0 | No | 2 |
| 13 | 0 | No | 1 |
| 4 | 2 | Yes | 1 |
| 15 | 0 | No | 2 |
| 16 | 5 | Yes | 1 |
| 17 | 4 | No | 3 |
| 18 | 0 | No | 2 |
| 19 | 6 | Yes | 2 |
| 20 | 0 | No | 2 |
| 21 | 3 | Yes | 1 |
| 22 | 0 | No | 1 |
| 23 | 2 | No | 1 |
| 24 | 3 | No | 2 |
| 25 | 5 | Yes | 2 |
| HRCT | Findings scored according to ICOERD-Classification | | |

Comment: in all cases no Empyhsema occurring

## Material and methods

A BioScout (B&S Analytik, Dortmund, Germany) consisting of a multi-capillary column (MCC) connected to an ion mobility spectrometer (IMS) was used, normally coupled to a SpiroScout (Ganshorn Medizin Electronic, Niederlauer, Germany) as $CO_2$-controlled sample inlet unit. The major parameters of the BioScout are summarized elsewhere [51–55] and briefly in Table 3. In the spectrometer a 550 MBq [56] Ni ß-radiation source was applied for the ionization of the carrier gas (synthetic air, Air liquid, purity 99,999 % Krefeld, Germany). It was connected to a polar multi-capillary column (MCC, type OV-5, Multichrom Ltd, Novosibirsk, Russia) used as the pre-separation unit. In this MCC the analytes of exhaled breath were sent through 1.000 parallel capillaries, each with an inner diameter of 40 µm and

**Table 2** Lung function findings

| Patient number | $FEV_1$ (% Predicted) | VC (% Predicted) | $FEV_1$/VC (%) | TLC (% Predicted) | Lung function-diagnosis | Diffusiontest result | BGA- finding |
|---|---|---|---|---|---|---|---|
| 1 | 106 | 103 | 77 | 97 | N | N | N |
| 2 | 55 | 59 | 68 | 80 | O and R | Td | N |
| 3 | 61 | 57 | 76 | 78 | O and R | Td | N |
| 4 | 105 | 101 | 77 | 99 | N | Td | N |
| 5 | 95 | 94 | 73 | 96 | N | Td | N |
| 6 | 89 | 86 | 77 | 83 | R | Td | N |
| 7 | 63 | 67 | 68 | 69 | O and R | Td | Hy |
| 8 | 50 | 44 | 82 | 60 | R | N | N |
| 9 | 107 | 94 | 83 | 91 | N | N | N |
| 10 | 95 | 92 | 73 | 88 | N | Td | N |
| 11 | 81 | 88 | 68 | 90 | O | Td | |
| 12 | 51 | 69 | 52 | 82 | O | Td | N |
| 13 | 50 | 60 | 63 | 111 | O and H | Td and Dd | N |
| 14 | 82 | 76 | 83 | 84 | N | Td | Hy |
| 15 | 101 | 101 | 73 | 107 | N | N | |
| 16 | 97 | 87 | 81 | 87 | N | Td | N |
| 17 | 129 | 100 | 97 | 85 | N | N | N |
| 18 | 85 | 89 | 70 | 108 | N | Td | N |
| 19 | 98 | 97 | 74 | 85 | N | Td | N |
| 20 | 33 | 31 | 78 | 57 | O and R | | |
| 21 | 77 | 79 | 72 | 81 | O and R | Td | N |
| 22 | 124 | 121 | 75 | 110 | N | N | Hy |
| 23 | 28 | 39 | 52 | 81 | O and R | Td | N |
| 24 | 79 | 78 | 75 | 88 | N | Td | N |
| 25 | 66 | 68 | 74 | 78 | R | Td | N |

*FEV1* Volume that has been exhaled at the end of the first second of forced expiration

*VC* Vital capacity: the volume of air breathed out after the deepest inhalation

*RV* Residual volume: the volume of air remaining in the lungs after a maximal exhalation

*TLC* Total lung capacity: the volume in the lungs at maximal inflation, the sum of VC and RV

Lung function diagnosis: *N* normal *O* Obstruction *R* Restriction

*Td* Transfer disorder

*Dd* Diffusion disorder

*BGA* Blood gas analysis

*Hy* Hypoxemia, oxygen partial pressure measured in the BGA below normal

a film thickness of 200 nm. The total diameter of the separation column was 3 mm.

The content of a sample loop of 10 mL was given to the inlet of the MCC and pumped into the IMS after preseparation directly connected to the ionization region of the IMS. The MCC and the drift tube IMS were held at 40 °C isothermal - in contrast to standard applications. The carrier and drift gas used was synthetic air (scientific quality, AIR LIQUIDE Deutschland, Düsseldorf, Germany).

With respect to the present investigations, a retention time of about 12 min was realized keeping the MCC adjusted at 40 °C. The measurements were taken for 12 min retention time.

The peaks were characterized using the software Visual Now (B&S Analytik, Dortmund Germany) which is described elsewhere [57–60]. All 83 peaks are characterized by their position with inverse reduced ion mobility (corresponding $1/K_0$-value) and retention time and their concentration related to the peak height (Fig. 1). Lung function findings data are obtained using Master Screen Body (Jäger, Software up 4.65c, version 4.65.2.0 release). Chest computed tomography were generated by G.E.® CT Discovery HD 750 64-slice, according to ICOERD-classification 45 (slice thickness 5 mm; 1,2 mm slice thickness reconstruction parameter, 10 mm maximum intensity projection [mip], scanning parameters 120 kV 70 m As ) in supine position.

**Table 3** Characteristics of ion mobility spectrometer (BioScout 2012)

| Parameter | BioScout |
|---|---|
| Ionisation source | $^{63}$Ni (550 MBq) |
| Electric field strength | 320 V/cm |
| Length of drift region | 12 cm |
| Diameter of drift region | 15 mm |
| Length of ionisation chamber | 15 mm |
| Shutter opening time | 300 µs |
| Shutter impulse time | 100 ms |
| Drift gas | synthetic air (20.5 % $O_2$ (4.5), 79.5 % $N_2$ (5.0)) |
| Drift gas flow | 100 … 300 mL/min |
| Temperature | room temperature |
| Pressure | 101 kPa (ambient pressure) |
| MCC | OV-5, polar |
| Column temperature | 40 °C, isothermal, adjusted |

## Results

The examinations of the control group and the study group were performed in the Knappschafts-Hospital (Dortmund) The peaks are compared to see a difference of peaks between the two groups. Here the IMS Set contains in total 37 measurements. Total 83 peaks were identified manually with the IMS-Chromatogram and statistically evaluated by the Wilcoxon-rank-sum test using VisualNow (B&S Analytik, Dortmund, Germany), see Table 4.

**Table 4** Single peaks analysis

| Name of Analyte | Peaks | Confidence level CL [%] | Sensitivity | Specificity |
|---|---|---|---|---|
| NN | P4 | 95 | 0,417 | 0,880 |
| Eucalyptol | P5 | 95 | 0,083 | 1,000 |
| 1-Pentanol | P12 | 95 | 0,250 | 1,000 |
| NN | P13 | 95 | 0,167 | 1,000 |
| n-Decane | P17 | 95 | 0,417 | 0,920 |
| 2-Ehtyl-1-hexanol | P29 | 95 | 0,167 | 1,000 |
| 1-Octanol | P30 | 95 | 0,167 | 1,000 |
| NN | P31 | 99 | 0,500 | 0,880 |
| Gamma-Terpinene | P36 | 95 | 0,833 | 0,680 |
| 3-Octanone | P38 | 99 | 0,500 | 0,920 |
| NN | P41 | 95 | 0,417 | 0,840 |
| NN | P42 | 95 | 0,083 | 1,000 |
| NN | P49 | 95 | 0,333 | 0,920 |
| 2-Octanol | P53 | 99 | 0,250 | 1,000 |
| 2-Heptanone | P57 | 95 | 0,250 | 0,920 |
| NN | P60 | 95 | 0,500 | 0,840 |
| NN | P64 | 95 | 0,333 | 0,920 |
| Phenylacetaldehyde | P65 | 95 | 0,333 | 0,880 |
| NN | P73 | 95 | 0,333 | 0,960 |
| NN | P77 | 95 | 0,500 | 0,920 |
| NN | P6b | 99 | 0,417 | 0,960 |
| 4-Ethyltoluol | P25b | 99,9 | 0,333 | 1,000 |
| Alpha-Pinene | P39b | 99,9 | 0,833 | 0,960 |
| 4-Heptanon_2 | P47b | 99 | 0,833 | 0,760 |
| Alpha-Terpinene | P74b | 99 | 0,667 | 0,800 |

*NN* not identified

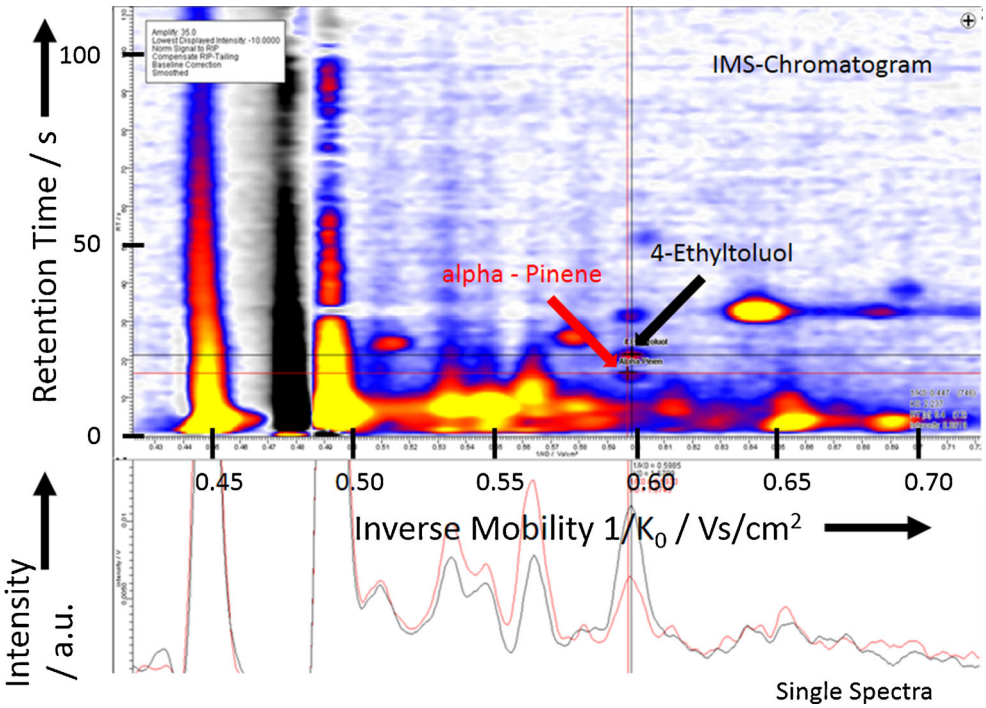


**Fig. 1** Two Peaks of the most discriminant analytes: 4-Ethyltoluol (*black*) and alpha pinene (*red*) IMS-Chromatogram (*above*), single spectra (*below*)

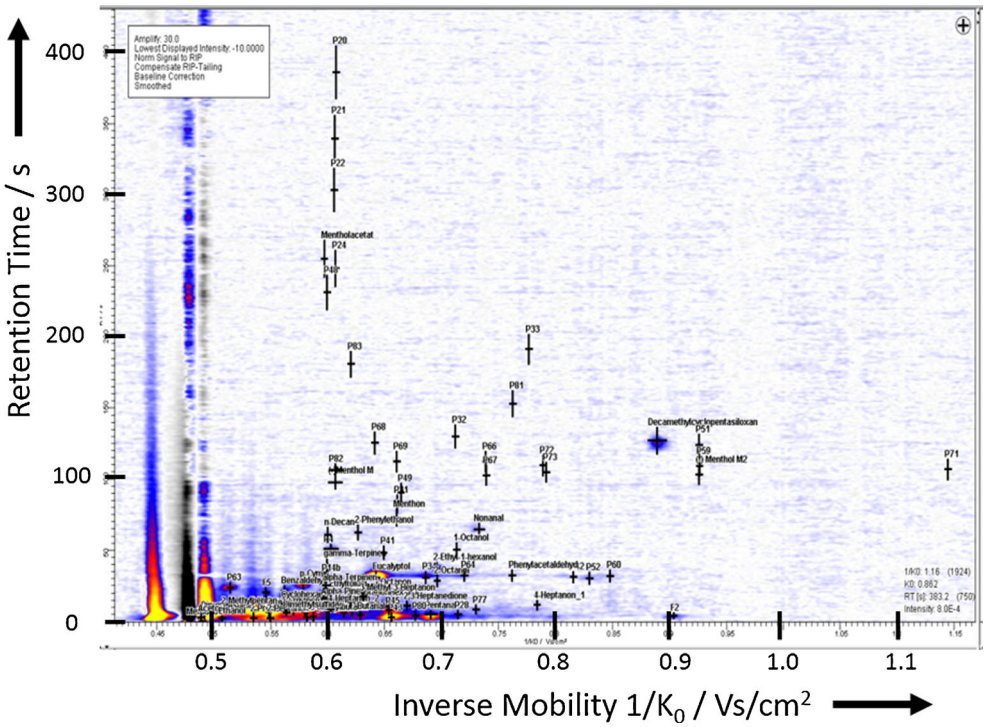


**Fig. 2** Typical MCC-IMS-Chromatogram with the layer of peaks investigated (83 at all peaks)

The differentiation of the peaks were possible by their drift and retention time values as shown in the Fig. 2 (IMS-chromatogram presenting the signals that were measured in the group of asbestos related diseases, decisions trees are shown in Fig. 3 (BK 4103). In addition Box-and-Whisker plots were performed to show the difference between the signals of patients with asbestos related disease and the controls—see Fig. 4.

In the next step a single peaks statistic was made that carried out 17 peaks with a confidence level of 95 %, five with 99 % and two with 99,9 %. For the single peaks statistics alpha pinene has a 99,9 % confidence level and a sensitivity of 83 % with a specificity of 96 %. Also 4-Ethyltoluol has a 99,9 % confidence level, but a sensitivity of 33 % and a specificity 100 %. In the rank sum alpha pinene is at position one and allows a clear differentiation of asbestos related disease from healthy persons in the decision tree with a signal intensity >0,004 as shown in Fig. 2. Alpha pinene, identified as peak P39b in the IMS-Chromatogram has a retention time 15,7 s and an inverse reduced ion mobility $1/K_0$=0,6 Vs/cm$^2$.

## Discussion

According to our knowledge this is the first study that compared the breath of patients with asbestosis and asbestos related pleural diseases (BK 4103) in common using the method of ion mobility spectrometry.

Chapman et al. [8] also summarized the results of the studies on exhaled breath in asbestos related disorders. The major components mentioned were 8-isoprostane, NO, 8-hydroxyl-2-deoxy-guanosine. It should be noted, that for

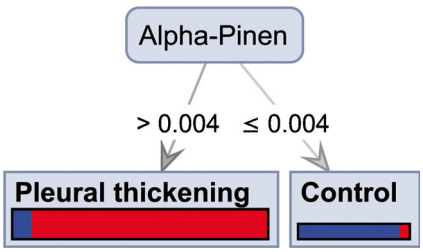


**Fig. 3** *Left*: decision tree to separate patients suffering of pleural thickening (in *red*, pleural thickening) to healthy controls (in *blue*, controls). Signal intensity of Alpha-Pinene > 0.004: pleural thickening, Alpha-Pinene ≤ 0.004: controls. *Below*: in the statistics by Rapid Miner the sensitivity for alpha pinene is 96 % and the specificity 50 %

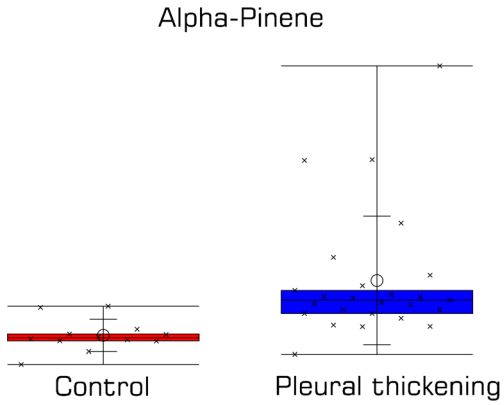


**Fig. 4** Box-and-Whisker Plot of best separating peak alpha pinene $p$<0.001 (99.9 %)

cases of application of electronic noses the nature of the analytes could not be found. In addition, the breath condensate was investigated mostly—totally different from direct breath analysis. Moilanen et al. [61] investigated NO in the breath condensate of patients with asbestosis using a Sievers NOA 280 analyser (Sievers Instruments, Boulder, Colorado, USA) and Ecoscreen condenser (Ecoscreen, Jaeger, Hoechberg, Germany) for the inflammatory marker leukotriene B4 and 8-isoprostane. They found that, "the mean (SE) alveolar NO concentration was significantly higher in patients with asbestosis than in controls". On the other hand also the level of leukotriene B4 and 8-isoprostane was higher in asbestosis patients in comparison to the healthy group as expression of the inflammation.

In the present study the breath samples of 37 persons (25 suffering of asbestos related diseases, and 12 healthy volunteers) were investigated using an IMS-MCC. The results showed that 83 signals could be collected in the patients'group. One of them was significantly higher in the patients with asbestos related diseases in comparison to the healthy persons. The peak with the trivial name p 39b could be identified as the volatile organic compound (VOC) alpha pinene. It may be possible that this compound could allow a discrimination between the patients with asbestos related diseases and healthy persons. One possible explanation for this finding is that that asbestosis and asbestos related pleural diseases are associated with chronic inflammatory reactions to inhaled asbestos fibres. Alpha pinene may reflect the existing inflammatory reaction in these patients, whereas any kind of inflammatory reaction (the inflammatory reaction caused by respiratory infections) at the healthy persons were excluded by physical examination, the questionnaire and the lung functional test.

Another point of view is the heterogeneous consistence of the patients group BK 4103. Here, they have nothing in common to each other concerning airways diseases except the fact, that they were exposed to asbestos with the follow of BK4103 diagnosis. Other potential factors of influence needs consideration within further studies. Nevertheless, the identified volatile organic compound allowed a discrimination of the patients with a sensitivity of 96 %, a specificity of 50 %, a positive predictive value of 80 % and negative predictive value of 86 %. On the other side we know that the BK 4103 isn't homogeneous in itself. The asbestosis is a pulmonary fibrosis with a connection to the airways whereas the pulmonary plaques or the pulmonary thickening has no. So how is it possible that all subgroups of BK 4103 have the same high intensity of alpha pinene in the exhaled breath although one is connected to the airways and the others are not? Therefore, the result provides further evidence that this is a subclinical inflammation caused by the fact of asbestos exposure?

Alpha pinene was found in the breath of normal humans by Philips et al. [62] using gas-chromatography coupled to mass spectrometry and by Libardoni et al. [63] applying a multi-bed sorption unit and two-dimensional gas chromatography. Ruzsany et al. [56] found relations of alpha-pinene to molds using ion mobility spectrometry. Vautz et al. [64] investigated the influence of humidity using UV ion mobility spectrometry. In addition, solid phase micro extraction was coupled to ion mobility spectrometry to detect gamma—Terpinene in various matrixes by Liu et al. [65], Wu [66] and Lai et al. [67].

Chapman et al. [8] summarized the studies of electronic nose devices in lung cancer, like GSMS, SPME/GC and PTR-MS—without direct relations to asbestos. Here, the conclusion was to develop non-invasive methods—as we realized with gaseous breath samples of 10 mL directly—and within less 12 min total analysis time.

## Summary

To differentiate between asbestos related diseases and healthy controls preliminary results were obtained using direct analysis of exhaled breath using ion mobility spectrometry. Breath samples of 10 mL of 25 patients suffering of Asbestos related diseases or occupational disease including patients with pleural thickening with and without pulmonary fibrosis were compared to those of 12 healthy controls. In total 83 peaks are found in the IMS-Chromatograms. A discrimination was possible with $p$-values <0.001 for two peaks (99.9 %) for alpha pinene and 4-ethyltoluol. The sensitivity was calculated to 96 %, specificity was low 50 %, positive and negative predictive values were 80 % and 86 %. The preliminary findings need further confirmation in larger population groups.

**Acknowledgments** A part of the work on this paper (JIBB) has been supported by Deutsche Forschungsgemeinschaft (DFG) within the Collaborative Research Center (Sonderforschungsbereich) SFB 876 "Providing Information by Resource-Constrained Analysis", project TB1 "Resource-Constrained Analysis of Spectrometry Data".

We want to thank to Berufsgenossenschaft Holz und Metall for the recruitment of patients, K.G. Hering and J. Rodenwald for the radiological assessment of the images and C. Kelbel for the pneumology expertise.

Notice: The work presented is part of the thesis of Y. Cakir [1, 3].

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