Marta Jäckel M.D. lieutenant-colonel:

Lung effects of different asbestos substitutes used by the industry

Review of PhD work

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Budapest, 2005

1 Background of the study

Lungs, first of all the bronchial mucosa are often places of malignant tumor development. Numerous epidemiological studies have proved that among the environmental risks of pulmonary carcinomas the inhalation of natural mineral fibers, mostly crocidolite asbestos, plays an important role (Becklake, 1976; Müller, 1981; Marczynski és mtsai, 1994). To avoid the health-damaging effects of asbestos, man made mineral fibers (MMMFs) were introduced. During the short period of their use the possible adversive effects have not been studied.

The toxicity of the above mentioned substances are determined by many factors, as the diameter (<3-3.5 micrometers), the length (<100 micrometers), the physicochemical and surface characteristics, the duration of exposure and the biopersistance. The analysis of these factors can help to reveal the late adversive effects of MMMFs.

2 The aim of the study

Asbestos-substitutes are widely used in the industry. During catastrophes and wars the sanation and reconstruction of damaged buildings are partly tasks of technical troops. If is therefore necessary to initiate studies for the sake of preventing possible health damaging effects.

The aims of the research

- Experimental studies on the effects of newly developed MMMFs and comparison of the obtained results with the well-known effects of asbestos.
- Development of new methods for analyzing the pathomechanism of asbestos and MMMFs
- After having learned the structure, geometry, elementary composition, biosolubility of MMMFs, and recognizing the least or none damaging sorts of fibers, to make propositions for the appropriate technical developments.

3 Presentation of the dust samples

The different MMMFs, developed to avoid the well known tumor inducing effect of asbestos, are anorganic isotrop fibers produced first of all from melted minerals, clay, slag, glass or pure natural oxides (slag wool, mineral wool, basalt wool, glass wool and microfibers as heat resistant ceramics).

4 Short review of the investigations

Wistar rats received instilled 2 mg of fibrous dusts suspended in 0.2ml saline. Lungs were formalin-fixed and paraffin-embedded at several intervals between 3-180 day after instillation. Structural changes were examined in hematoxylin-eosin-stained sections.

Histochemical reactions were performed to reveal changes of the mucus production (alcian-blue-PAS), the production of collagen fibers (picrosyrius red), the remodellation of the elastic fibers (resorcin-fuschin) and the accumulation of iron (Prussian-blue).

Immunhistochemical reactions were introduced to reveal damages of the basement membranes.

Morphological characteristics and elementary composition of the fibers were examined by scanning electron microscope (OPTON DSM 950) and connected LINK energy-dispersive x-ray spectrometer (EDS) as well as by Oxford Instruments EDS ISIS. Transmission electron microscopy (JEOL 100B) revealed the subcellular changes in the lung tissue. The localization of different elementary components in the structure was examined by the mapping function of the EDS.

With the help of neutron activation ppm amounts of elements were detectable in the fibers.

In vitro biosolubility was examined in 0.1M phosphate-buffer at pH 4.5 and 7.4 and the dissolved elements were detected by EDS analysis.

5 General conclusions

According to the theory of fiber carcinogenicity the adversive effects of fibrous dusts depend first of all on geometry and biopersistance. The MMMFs, developed to substitute the fibrogenic and carcinogenic natural mineral fibers, produce less dust but the small fractions

released into the area of gas exchange make us ponder over the question of potential adversive effects. In case of identical geometry, different tissue effects can be found only in case of different biopersistency and elementary composition.

Among the asbestos substitutes developed in the last decades the dust of glass wool proved to be the most biosoluble in the lung tissue. Profound and reliable examination of the biosolubility is possible only in animal experiments, where the time of exposition and the environmental circumstances are standardized, and no other disturbing factors as smoking or other types of dusts make the results uncertain.

Concentration, geometry and biopersistence are the three most important factors of carcinogenecity (KGB criteria in the German literature).

The geometry of the fibers decides the place of impact in the bronchi. More than 51% of inhaled fibers with >12 μm aerodynamic diameter (the geometric diameter approximately >4 μm) are deposited on the mucosa of the nose, pharynx and larynx. In case of an appropriately small geometric diameter fibers of 100μm length can also enter the alveoli. The overwhelming majority entering the alveoli in humans is shorter than 5μm. First of all fibers exceeding 10μm length are carcinogenic, while the carcinogenicity of fibers with 2-3μm length is negligible. Particles with a geometric diameter less than 3μm and with a length/diameter ratio greater than 5:1 are „crucial". Particles longer than 5μm and less than 3μm in diameter, with a length/diameter ratio greater than 3:1 are the WHO fibers. To avoid these types of particles is of great importance at the work place. Apart from the endless MMMFs all types of asbestos substitutes reveal a wide spectrum of diameters, given by the productions technology, from which only 0.5% of dusts are WHO particles. The percentage of WHO particles and, in parallel, the dust production is inversely proportional to the mean fiber diameter. The decisive parameter in the classification of fibers from the viewpoint of safeguarding workers is the average diameter.

The biopersistance depends on in vivo dissolution and break down as well as on physical elimination. It is easy to understand that the probability of tissue damage and development of tumors is the greater the longer the effect of dust is on the lung tissue and serosa. Upon appraisal of the results of animal experiments we should take into consideration that physical clearing is more intensive in rats than in man, but the intrapulmonary milieu and the dissolving effects of tissue fluid are identical.

Among the asbestos substitutes used in the past decades, glass wool proved to be at least resistant against the tissue fluids. Biosolubility of the B0901 glass fiber, developed newly in Germany, is much quicker than that of the traditional ones.

Studies on dust-induced tumor rat experiments are preferred. The aim of our experiments was to study glass wool biosolubility and tissue reactions in the lungs, connective tissue and mesothelial cells of the peritoneum 3-180 days following intratracheal instillation and subcutaneous or intaperitoneal injection in rats.

Many kinds of dusts induce inflammatory reaction in the lungs, particularly if in large amounts. Repeated inflammations lead to the extended fibrous remodeling of the lungs. Fibrosis develops not only following the inhalation of quartz but also as a late consequence of asbestos inhalation (asbestosis). Some of the natural mineral fibers (asbestos, erionite) lead to development of bronchial, pleural and peritoneal tumors in humans.

Our knowledge on the pathomechanism of tumoral transformation is not sufficient. In all probability the reactive oxygen radicals play a decisive role reacting with the DNA of the nuclei. The production of reactive oxygen radicals is promoted not only by the inflammatory processes, but also by the catalyzing effects of superficial metal ions.

Finally, it should not be left unconsidered that increased proliferative activity of the healing process of mechanically damaged tissues makes the dividing cells quite sensitive against mutation inducers and the reparative proliferation may become tumorous.

Many MMMFs have been introduced as substitutes for carcinogenic asbestos. These might be endless fibers (glasstextil fibers), mineral fibers (glass-, stone-, slag-wools), glasslike ceramic fibers and fibers developed for special employment (e.g. glass microfibers). Our experiments were initiated in order to examine various fibers previously reported to have carcinogenic effects (Nies, 1998).

Exposure to dusts with fibrous structure, especially in case of asbestos, induces increased amounts of connective tissue in the interstitium as well as malignant tumors of the epithelium and mesothelium. Epidemiological studies of the last 40 years revealed that crocidolite, amosite and tremolite belonging to the amphibole group of asbestos induce fibrosis and malignancies far more frequently than crisotile belonging to the serpentine group. In our experiments we found that the asbestos fibers are different not only in respect to their morphology, but also according to their biopersistence. This means that the amphiboles are

found in the lung tissue for a longer period of time, thus being far more bioresistant than crisotile (Mc Donald JC, 1998).

The experiments proved that the inhalation of the conventional and biosoluble glass fibers caused no detectable lung fibrosis and neither adenomatoid bronchial epithelial proliferations, nor malignant lung tumors developed. In consistence with the human experiences (Gibbs et all, 1997.) hardly any glass fibers were found in the lungs of the glass wool-instilled animals. We could not find significant amounts of glass-indicative elements after instillation of conventional glass fibers in the lung tissue. In case of biosoluble glass fibers the neutron activation analysis revealed the presence of arsenic and antimony in the lung tissue. This might be the cause of the development of tuberculoid granulomas in the instilled lungs. One should consider whether the quick solution of glass fibers is desirable for the lung and for the whole organism. The lung damaging effects of glass fibers is much less than that of asbestos, however, according to our experiments and the latest recommendations of WHO, one cannot give a minimum of dust load without possible biological consequences (Kerényi és mtsai, 1998).

Neither the conventional nor the biosoluble glass fibers damage the mesothelial cells to a degree of having to fear of any tumor development.

Tuberculoid reaction found in one quarter of the animals is probably a type IV immunoreaction and needs further investigations.

The coating of the glass wool motivated by reasons of production and use does not influence the pethogenicity, phagocytosis, biosolubility or elimination of the fiber.

6 New scientific results

1. My work contributed to the clarification of the fundamental tissue damaging mechanism of asbestos substitutes, proving the slight or no pathogenic effects of glass fibers in comparison to asbestos.
2. The in vitro method for the detection of biosolubility was developed by me.
3. As a result of the experiments carried out in laboratories both in Hungary and abroad it is possible to give a hierarchy of asbestos substitutes according to their pathogenicity.
4. Besides the concepts of biosolubility and biopersistence it might be useful to introduce the concept of biocompatibility to qualify the asbestos substitutes in Hungary.

7 Employment of the results and recommendations

The presently discussed results and their conclusions are of interest to the experts of industrial innovations, occupational and military hygiene and also in the medical field since

- during the short exposure, limited by the life expectations of rats, the MMMFs were unable to damage the lung tissue to a degree, which can induce fibrosis or tumoral transformation.
- contrary to the findings on asbestos, MMMFs most probably do not cause fibrosis or malignancies even after a longer period of time.

According to my opinion, the results reported in this paper might be useful in military health prevention as well as in judging doubtful cases of occupational hygienic. The results might also be helpful in choosing appropriate insulation materials for special demands and last but not least, might further stimulate research studies.

8 Publications:

Papers in edited book:

1. Jäckel, M., Kerényi, T.:
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   (Környezeti ártalmak és a légzőrendszer IV. kötet, 160-162.1994.)

3. Adamis, Z., Kerényi, T., Jäckel, M., Tátray, E., Ungváry, Gy.:
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   (Környezeti ártalmak és a légzőrendszer IV. kötet, 4-6. 1994.)

4. Kerényi T., Voss, B., Müller, K-M., Jäckel, M.:
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   (Környezeti ártalmak és a légzőrendszer IV. kötet, 69-72. 1994.)

5. Kerényi, T., Jäckel, M., Voss, B., Müller, K-M.:
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6. Jäckel, M., Kerényi, T., Voss, B., Wiethege, T.:
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   (Környezeti ártalmak és a légzőrendszer V. kötet, 80. 1995.)

7. Jäckel,M., Kerényi,T., Voss,B., Wiethege, Th.:
   A bronchusepithel reaktív proliferációja rostos porok kísérletes instillációja után
   (Környezeti ártalmak és a légzőrendszer VI. 67-71. 1996.)

8. Kerényi,T., Voss,B., Grasbon,S., Jäckel,M., Müller,K-M.:
   Krokidolit azbeszt hatása a savós hártyákra
   (Környezeti ártalmak és a légzőrendszer VI. 88-92. 1996.)

9. Kerényi,T., Jäckel,M., Voss,B., Müller,K.M.:
   A tüdőszövetben felhalmozódó, rostos porok vizsgálata humán anyagon
   (Környezeti ártalmak és a légzőrendszer VII. Eds: Szabó,T., Miriszlai,E. 43-47. 1997.)

10. Jäckel,M., Kerényi,T., Cserba A.:
    A tüdő és a pleura porbelégzéssel kapcsolatos tumorai
    (Környezeti ártalmak és a légzőrendszer VII. Eds: Szabó,T., Miriszlai,E. 25-27. 1997.)

11. Kerényi,T., Jäckel,M., Sáfrány,Á., Hargittai,P., Tóthné,K.,K., Csonka,F.:
    Üveggyapot tüdőkárosító hatásainak kísérletes vizsgálata
    (A környezeti ártalmak és a légzőrendszer VIII. 1998.93-96.)

12. Jäckel M., Kerényi T., Sáfrány Á., Hargittai P., Tóthné, Kiss K., Csonka F., Pott F.:

A hagyományos és biosolubilis üveggyapotok tüdőre gyakorolt hatásának vizsgálata kísérleti állatokban (Környezeti ártalmak és a légzőrendszer IX. 48-53. 1999.)

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A gumipor tüdő- és szövetkárosító hatásainak kísérletes vizsgálata (Környezeti ártalmak és a légzőrendszer IX. 54-63. 1999.)

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A biosolubilitás és a bioperzisztencia szöveti következményei
(Környezeti ártalmak és a légzőrendszer XI. kötet 115-124. 2001.ISBN 963 04 3904 2 Ö)

15. Kerényi,T., Huszár, A., Sáfrány,Á., Hargittai,P., Mózsa,Sz., Korényi-Both A., Illyés,Gy., Jäckel,M.:
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16. Jäckel,M., Kerényi,T.:
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18. Kerényi,T., Adamis,Z., Jäckel,M.:
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(Környezeti Ártalmak és a Légzőrendszer XIII. 2003. 191-200. old. ISBN 9630439042Ö)

19. Jäckel,M., Bartók,K., Abermann,G., Kerényi,T.:
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20. Kerényi,T., Hargitai,P., Jäckel,M., Sáfrány Á.:
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Ásványi rostok bronchuskárosító hatásainak összehasonlító kísérletes vizsgálata
(Medicina Thoracalis, 49. 317-325. 1996.)

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2. Moldvay,J., Jäckel,M., Bogos,K., Soltesz,I., Agocs,L., Kovacs,G., Schaff,Z.:
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3. Jäckel,M., Sáfrány,Á., Hargittai,P., Szőke,R., Pott,F., Kerényi,T.:
Lung effects of conventional and biosoluble glass fibers as asbestos substitutes. An experimental study.
(AARMS, Vol. 4, No. 2 (2005)275-283

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Azbeszt okozta kísérletes bronchuslaesiok
(Első Eurázsiai Orvostudományi Kongresszus, Győr, 1994.)

2. Kerényi,T., Voss,B., Jäckel, M., Wiethege, T., Müller, KM.:
Asbestos and man-made mineral fibers induced bronchial lesions
(XIII. National Congress of the Hungarian Society for Occupational Health with International Participation,
Budapest, 1995. okt.4-6)

3. Jäckel,M., Kerényi,T., Voss,B., Wiethege, T.,:
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(XIII. National Congress of the Hungarian Society for Occupational Health with International Participation,
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4. Kerényi,T., Voss,B., Jäckel,M., Müller, K-M.:
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9. Pápay,J., Jäckel,M., Moldvay,J.:
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10. Jäckel,M., Moldvay,J., Bogos,K., Soltész,I., Agócs,L., Kovács,G., Schaff,Z.:
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12. Kerényi,T., Jäckel,M., Szacsky,M., Molnár,Z., Balla,M., Voss,B.:
Lung effects and biosolubility of different glass fibres
(The European Respiratory Journal ERS Annual Congres . 446p. 2001.IF: 2,59)

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The role of TTF-1 in differentiating primary and metastatic lung adenocarcinomas
(Lung Cancer, Vol. 41. Suppl. 2. August 2003. S254)

15. Jäckel,M., Sáfrány,Á., Hargittai,P., Illyés,Gy., Kerényi,T.:
Lung damages after inhalation of organic substance-contaminated sand
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16. Jäckel,M., Moldvay,J., Bogos,K., Soltész,I., Agócs,L., Kovács,G., Schaff,Zs.:
Thyroid transcription factor-1 (TTF-1) in the differential diagnosis of the primary and metastatic lung cancer. Our 4-year follow-up study
(Virchows Archiv Vol.447 No.2 August 2005 p. 312-313)

9 Curriculum vitae

Marta Jäckel M. D. was born in Budapest, Hungary, 21st March 1957.

General medicine studies 1975-81 Semmelweis University of Medicine, Budapest, Hungary.
Graduated in medicine at the Semmelweis University of Medicine in 1981
Specialisation in general practice 1986
in pathology 1994
in catastrophe and military medicine 1996
in cytopathology 2002

Appointments:

1981-1983 air-force doctor in the Military Airport of Hungarian Defence Forces in Szentkirályszabadja (2nd lieutenant)
1983-1986 chief of the Health Department of 2nd Recruiting Centre of Hungarian Army in Veszprém (1st lieutenant)
1986-1997 adjoint in the Central Hospital of Hungarian Defence Forces, Department of Pathology in Budapest (major)
1997-2002 adjoint professor in the Semmelweis University Budapest, 2nd Department of Pathology
2002- 2005 specialist in the Central Hospital of Hungarian Defence Forces, Department of Pathology in Budapest lieutenant colonel)

Abroad activities: 1994 April-July: Berufsgenossenschaftliches Forschungsinstitut für Arbeitsmedizin, Abteilung für Medizinische Biologie, Bochum-Germany

1998. Sept-Dec. Klinikum der Albert Ludwigs Universität, Pathologisches Institut,
Freiburg-Germany

2000 Oct.-2001 Sept: Invitation to the University of Minnesota, Minneapolis

Research activities: pulmonary effects of asbestos and different man-made mineral fibers (comparative study of reactive and neoplastic lesions, biodegradation of man-made mineral fibres, biosolubility of different types of glasswool)

arteriosclerosis research (different phenotype of smooth muscle cells in the artery wall)

Memberships of scientific societies: Hungarian Society of Pathologists
Hungarian Society of Pulmonologists
International Academy of Pathology –Hungarian Division
European Respiratory Society