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Inflammation markers in the serum of salt miners

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The inflammation markers alpha-1-antitrypsin (AAT), Clara cell protein (CC-16), soluble interleukin-2-receptor (IL-R) and the soluble adhesion molecule E-selectin, the intercellular adhesion molecule (ICAM-1) and the vascular adhesion molecule (VCAM-1) were determined in the serum of 195 salt-exposed miners to analyse dose–response relationships between markers and potash dust. Alpha-1-antitrypsin, Clara-cell protein, IL2-R, E-selectin and VCAM-1 were not changed by salt exposure, however the ICAM-1 level in the serum fell slightly as the salt exposure increased. This effect was strongest in the group of smokers, still visible in the group of ex-smokers, no effect was seen in non-smokers. Markers, with the exception of VCAM-1, were influenced by tobacco exposure. Since markers were not elevated in relation to salt dust exposure, the results do not support an inflammatory effect of potash dust on the respiratory system.

Keywords: inflammation markers, potash dust, tobacco exposure.

Abbreviations: AAT, alpha-1-antitrypsin; CC-16, Clara cell protein; es, ex-smoker (non-smoker for at least 1 year); FVC %, forced vital capacity in percent of normal value; ICAM-1, intercellular adhesion molecule; IL-R, interleukin-2-receptor; ns, non-smoker; s, smoker; VCAM-, vascular adhesion molecule.

Introduction

Prevention of occupational lung diseases could be more effective if early diagnosis by determination of other markers, e.g. indicators of inflammation, is done complementary to lung function tests. Inflammation markes in the serum may be changed after exposure to irritants or allergens, and can thus be used as sensitive tools to monitor adverse effects on the respiratory system. This was the reason for analysing inflammation markers in the serum of potash-exposed miners in addition to changes in lung function (Lotz *et al.* 1997, 1998) during a study which looked at the effect of salt dust on miners. The results of this study by Lotz *et al.* suggest that high concentrations of soluble dust over a working life slightly decrease the lung function parameters FVC and FEV1. Additional factors of exposure in underground working are diesel exhaust and nitrogen dioxide, but the different effects of these factors could not been identified because of the high intercorrelation of these factors with salt dust. These results are comparable to the results of other studies indicating higher rates of bronchitis and partially decreased lung function in salt miners (Regenspurger 1966, Possner 1967, Markham and Tan 1981, Attfield *et al.* 1982, Graham *et al.* 1984, Hohbein 1989). No information was

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found in the literature concerning the effect of potash exposure on inflammation markers.

This part of the study describes the effect of salt dust on inflammation markers, additionally the effect of tobacco exposure on inflammation markers was analysed to further examine their value as effect markers after exposure to irritants.

The following parameters were selected because data in the literature show that they are changed after exposure to irritants or allergens and/or in patients with airway diseases (table 1):

Alpha-1-antitrypsin, which is the most important protease for the lung defence system (Carell 1990).

Clara cell protein which is a natural immunoregulator protecting the respiratory system by control of inflammation. The protein is secreted by Clara cells, non-ciliated cells in the bronchioles (Massaro 1987, Lesur *et al.* 1995, Dierynck *et al.* 1996).

Interleukin-2 receptor which is expressed on activated T-cells, and shed into the serum during immune activation (Rubin and Nelson 1990). Intercellular adhesion molecule, the vascular adhesion molecule and E-selectin which are receptors for leukocytes, expressed on endothelial cells and facilitate the influx of leukocytes to sites of inflammation (Gearing *et al.* 1992, Canonica *et al.* 1994, Hamacher and Schaberg 1994).

Methods

Serological investigation

Out of the original cohort of 402 salt miners 195 were examined by serological methods (the 195 miners were comparable to the total group of 402 regarding age, smoking habits and salt exposure). since the investigated markers are not specific for inflammations of the respiratory tract, sera from persons with other inflammatory diseases (rheumatic diseases, psoriasis, atopic eczema, urticaria, infectious diseases, autoimmune diseases, inflammatory diseases of the gastrointestinal tract) had to be excluded. Blood was collected and centrifuged after 2 h clotting time at room temperature. Serum was frozen in small aliquots to prevent repeated freezing and thawing and stored at –20 °C. Sera were analysed within 6 months. Parameters ICAM-1, VCAM-1, E-selectin and IL2-R were analysed in 195 sera using ELISA systems according to the manufacturer's instructions (see table 2). The same batch number was used for all samples. Alpha-1-antitrypsin was investigated in 112 sera by nephelometry. Measurement of the Clara cell protein was performed in the laboratory of Prof. Bernard (Bernard *et al.* 1991) by immunoassay in a selected sample of $n = 41$. There were technical reasons for analysing smaller samples for alpha-1-antitrypsin and the Clara cell protein. With regard to age, smoking habits and salt exposure the smaller groups were comparable to the group of $n = 195$. Table 2 summarizes the numbers of sera investigated, intra-individual coefficient of variation and origin of assay.

Exposure assessment

Salt dust was measured by two-step gravimetry. Individual lifetime exposure values were calculated for all miners. Mean individual dose of inhalable dust (defined as the mass fraction of inhaled particles, which is inhaled through the nose and mouth) was 4446 mg m^{-3} × months (range 360–17171 mg m^{-3} × months) and of respirable dust (defined as the mass fraction of inhaled particles penetrating through the unciliated airways) 609.85 mg m^{-3} × months (range 57.6–1942 mg m^{-3} × months). The amount of diesel exhaust was estimated to be 5 ± 29 mg m^{-3} × months. Only a few short time values measured by indicator tubes were available for nitrogen dioxide. They could not be used for individual lifetime exposure values.

Statistical analysis

Group differences between smokers, ex-smokers and non-smokers were analysed by the *t*-test, dose–response relationships were calculated by partial correlation and/or regression analysis. Statistical analysis was carried out with SPSS, Version 6 (Munich, FRG).

Table 1. Inflammation markers, serum level or cell expression following exposure to irritants and allergens–inflammation markers and obstructive airway diseases.

Exposure/marker	AAT	CC-16	IL2-R	E-selectin	ICAM-1	VCAM-1
Tobacco smoke	↑ Splettstösser *et al.* 1990	↓ Bernard *et al.* 1992b Shijubo *et al.* 1997	↑ Tollerud 1994 Ginns *et al.* 1990	= Schaberg *et al.* 1996	↑ Schaberg *et al.* 1996	= Schaberg *et al,* 1996
Ozone	↑ Devlin *et al.* 1991	↑ Dodge *et al.* 1994 Hong 1996			2 ↑ Beck *et al* 1994 Takahashi *et al.* 1995	
Allergens			↑ Virchow *et al.* 1995	↑ Zangrilli *et al.* 1995 Kato *et al.* 1995	↑ Zangrilli *et al.* 1995	↑ Takahashi *et al.* 1994
Asthma/rhinitis			↑ Matsumoto *et al.* 1994	↑ Montefort *et al.* 1994 Gosset *et al.* 1995 Hirata *et al.* 1998		↑ Kobayashi *et al.* 1994 Hirata *et al.* 1998
Bronchitis		↓ Bernard *et al.* 1992a		↑ Rise *et al.* 1994	↑ di Stefano *et al.* 1994	

↑ Increased level/expression versus controls; ↓, decreased level/expression versus controls; = no change versus controls; 1 results proven in animal models or 2 human cell lines.

Table 2. Methods used to analyse inflammation markers.

Marker	Number of sera	Coefficient of variation (%)	Origin of assay
AAT, g l^{-1}	112	2	Beckmann Instruments
CG-16, µg l^{-1}	41	8	Bernard 1991, 1997
IL2-R, U ml^{-1}	195	13.9	Milenia, Biermann
E-selectin, ng ml^{-1}	195	8.5	R + D Systems
ICAM-1, ng ml^{-1}	195	3.7	T-Cell Diagnostics
VCAM-1, ng ml^{-1}	195	9.7	R + D Systems

Results

Table 3 shows mean values, standard deviation and range of inflammation markers, and coefficients of variation for the methods that have been used. Mean values of inflammation markers were comparable to the values obtained by analysis of sera from blood donors, carried out as described in the manufacturer's instructions.

Out of the six inflammation markers only ICAM-1 was affected by potash exposure (table 4). As shown by regression analysis, the ICAM-1 level was lowered as the salt exposure increased. ICAM level was lowered in smokers and in ex-smokers with a higher salt exposure, no effect was seen in non-smokers (table 5), but the decrease of ICAM-1 was low. No correlation was found between diesel exhaust and inflammation markers (table 6).

Significant differences were found for alpha-1-antitrypsin between smokers and non-smokers as well as between smokers and ex-smokers. There was a trend to lower Clara cell protein levels in smokers compared with non-smokers and ex-smokers and a correlation to the number of pack-years. The adhesion molecule E-selectin was increased in smokers and ex-smokers compared with non-smokers, levels in smokers correlating to the number of smoked cigarettes per day. Very distinct differences between the serum level of ICAM-1 in the three groups were seen, ICAM-1 level was significantly higher in smokers than in non-smokers and ex-smokers. Correlation was found between ICAM serum levels in smokers and pack-years as well as the number of cigarettes smoked per day. Levels of IL2-R and VCAM-1 in serum did not significantly differ between the three groups (tables 7 and 8).

Discussion

AAT, CC-16,. IL2-R and E-selectin are not changed by potash dust, as has been reported for other types of exposure. Elevated levels of AAT in the BAL of healthy subjects following ozone exposure have been described (0.1 ppm) by Devlin *et al.* (1991). Epidemiological studies comparing AAT serum levels of women in areas with different air pollution show, that AAT serum levels tend to be higher in more polluted areas (Neuhann *et al.* 1994, Stiller-Winkler *et al.* 1996). Elevated CC-16 levels have been reported following exposure to ozone (Dodge *et al.* 1994, Hong 1996) and asbestos (Lesur *et al.* 1996), lower CC-16 concentrations were found in silica-exposed persons (Bernard *et al.* 1994). Our results suggest that the ICAM-1 serum level is slightly decreased with higher salt exposure, this effect was most evident in smokers. In the literature, however, an increased expression of adhesion molecules on nasal epithelial cells and bronchial epithelial cells has been

Table 3. Mean values, standard deviation, range and coefficient of variation.

Marker	Mean value	Standard deviation	Range	Interindividual coefficient of variation (%)
AAT, g l^{-1}	1.4	0.2	0.91–2.0	14
CG-16, μg l^{-1}	16.9	5.8	6.7–33.1	34
IL2-R, U ml^{-1}	378	135	135–192	35
E-selectin, ng ml^{-1}	54.8	20.8	3.4–130	37
ICAM-1, ng ml^{-1}	341	79.4	172–635	23
VCAM-1, ng ml^{-1}	659	179	326–1562	27

Table 4. Effect of cumulative salt exposure (dose) on inflammation markers (regression analysis[a])

	Respirable dust (mg m^{-3} × months)		Inhalable dust (mg/m^{-3} × months)	
Marker	Coefficient of regression	*p*-value	Coefficient of regression	*p*-value
AAT, g l^{-1}	–0.000075	0.06	–0.0000075	0.14
CG-16, μg l^{-1}	0.002	0.13	0.0003	0.25
IL2-R, U ml^{-1}	0.001	0.96	0.00076	0.77
Selectin, ng ml^{-1}	–0.001	0.12	0.00026	0.50
ICAM-1, ng ml^{-1}	–0.0039	0.07	–0.004	0.01
VCAM-1, ng ml^{-1}	–0.0027	0.95	–0.00045	0.89

[a] Other variables included in the regression model: age, height, body mass index, relative weight, smoking (yes/no), inflammatory respiratory diseases in the past, coronary diseases, other types of exposure before working in the salt mine.

Table 5. Effect of cumulative salt exposure (dose) on ICAM-1 serum level in the group of non-smokers, ex-smokers and smokers (regression analysis[a])

	Respirable dust (mg m^{-3} × months)		Inhalable dust (mg m^{-3} × months)	
	Coefficient of regression	*p*-value	Coefficient of regression	*p* -value
Non-smoker ($n = 44$)	–0.013	0.47	–0.002	0.30
Ex-smoker ($n = 81$)	–0.039	0.03	–0.003	0.08
Smoker ($n = 70$)	–0.070	0.03	–0.009	0.06

[a] Other variables included in the regression model: age, height, body mass index, relative weight, inflammatory respiratory diseases in the past, coronary diseases, other types of exposure before working in the salt mine.

described after ozone inhalation (Beck *et al.* 1994, Takahashi *et al.* 1995). Elevated levels of the adhesion molecules (ICAM-1, E-selectin, VCAM-1) were observed after allergen provocation (Takahashi *et al.* 1994, Zangrilli *et al.* 1995, Hirata *et al.* 1998). The decreasing ICAM-1 values following salt dust exposure, suggesting an anti-inflammatory effect, are also in contrast to findings obtained by analysis of relationships between potash exposure and lung function parameters. A decrease of FVC%N was observed which was dependent on respirable dust dose (coefficient of regression = –0.0027, $p = 0.06$)and inhalable dust dose (coefficient of regression = –0.00038, $p = 0.03$) (Lotz *et al.* 1997).

A release of cytokines from epithelial cell lines (Steerenberg *et al.* 1988) and rat

Table 6. Effect of diesel exhaust dose (mg m^{-3} × months) on inflammation markers (regression analysis[a]).

Markers	Coefficient of regression	*p*-value
AAT, g l^{-1}	–0.00044	0.41
CG-16, μg l^{-1}	0.0028	0.31
IL2-R, U ml^{-1}	0.09	0.75
Selectin, ng ml^{-1}	–0.037	0.16
ICAM, ng ml^{-1}	–0.22	0.38
VCAM-1, ng ml^{-1}	–0.154	0.68

[a] Other variables included in the regression model: age, height, body mass index, relative weight, smoking (yes/no), inflammatory respiratory diseases in the past, coronary diseases, other types of exposure before working in the salt mine.

Table 7. Mean level of inflammation markers in non-smokers, ex-smokers and smokers (*t*-test).

Marker		Non-smoker (ns)	Ex-smoker (es)	Smoker (s)	*p*-value	
AAT	g l^{-1}	1.34	1.40	1.50	ns/s	0.00
ns	$n = 24$				ns/es	0.20
es	$n = 42$				es/s	0.01
s	$n = 53$					
CC-16	μg l^{-1}	18.3	18.1	14.7	ns/s	0.06
ns	$n = 7$				ns/es	0.95
es	$n = 13$				es/s	0.10
s	$n = 21$					
IL2-R	U ml^{-1}	356	364	400	ns/s	0.06
ns	$n = 44$				ns/es	0.81
es	$n = 81$				es/s	0.13
s	$n = 70$					
E-selectin	ng ml^{-1}	47.7	54.8	54.5	ns/s	0.06
ns	$n = 44$				ns/es	0.05
es	$n = 81$				es/s	0.93
s	$n = 70$					
ICAM-1	ng ml^{-1}	314	317	377	ns/s	0.00
ns	$n = 44$				ns/es	0.78
es	$n = 81$				es/s	0.00
s	$n = 70$					
VCAM-1	ng ml^{-1}	680	664	627	ns/s	0.11
ns	$n = 44$				ns/es	0.65
es	$n = 81$				es/s	0.22
s	$n = 70$					

alveolar macrophages (Yang *et al.* 1997) that have been exposed to diesel exhaust have been described, however no relationship was found between the inflammation markers analysed in this study and diesel exhaust. Since diesel exhaust exposure was highly correlated to salt exposure the lack of a relationship to inflammation markers was not unexpected.

Smoking seems to have an effect on serum levels of inflammation markers AAT, CC-16, ICAM-1 and E-selectin. These results support data reported in the literature and confirm their value as useful markers for an adverse effect after

Table 8. Correlation of inflammation markers and tobacco exposure in smokers (partial correlation[a])

Marker	Pack-years		Number of cigarettes per day	
	Coefficient of correlation	*p*-value	Coefficient of correlation	*p*-value
AAT, g l^{-1} $n = 53$	0.222	0.06	0.160	0.17
CC-16, µg l^{-1} $n = 21$	–0.485	0.06	–0.277	0.30
IL2-R, U ml^{-1} $n = 70$	–0.092	0.46	–0.131	0.30
E-selectin, ng ml^{-1} $n = 70$	0.153	0.22	0.243	0.05
ICAM-1, ng ml^{-} $n = 70$	0.298	0.02	0.296	0.02
VCAM-1, ng ml^{-1} $n = 70$	–0.012	0.92	–0.101	0.42

[a] Adjusted for the variables: age, body-mass index, relative weight, inhalable dust concentration.

exposure to irritants. In the sera of smokers, elevated levels of AAT have also been reported by Splettstösser *et al*. (1990). Our study shows elevated levels of the adhesion molecules E-selectin and ICAM-1 in smokers dependent on pack years or the number of cigarettes smoked. This could be explained by an activation of alveolar macrophages, leading to secretion of mediators such as TNF-alpha which induces the expression of adhesion molecules. Also Grothey *et al*. (1998) have described elevated ICAM-1 levels in the sera of smokers. Increased expression of E-selectin in bronchial biopsies of smokers and ex-smokers versus non-smokers is suggested by Turato *et al*. (1995), which is in agreement with our results. Schaberg *et al*. (1996) however could not find increased E-selectin expression in smokers. Elevated ICAM-1 levels in smokers are in agreement with the immunohistological results reported by Schaberg *et al*. (1996) and Turato *et al*. (1995). In contrast to our study Turato *et al*. could not find a difference between ICAM-1 serum level in smokers and ex-smokers. However, results obtained by immunohistological techniques are difficult to compare to serological investigations since the cellular source of soluble adhesion molecules cannot be verified. Other investigators analysing ICAM-1 and/or E-selectin levels in the serum were not able to find differences between smokers and non-smokers, which might, for instance, be explained by different cohort characteristics, e.g. patients with sarcoidosis (Ishii and Kitamura 1995) or bronchitis (Riise *et al*. 1994).

Since AAT, CC-16, IL2-R and E-selection were not changed and the ICAM-1 level was slightly lowered by potash exposure, the results obtained for the inflammation markers do not support the suggestion of an adverse effect of potash dust on the respiratory system. Additionally an inflammatory effect of diesel exhaust could not be verified by these markers. A relationship was found between lung function parameters and salt dust exposure. However, the effect of salt exposure on lung function was also low and there was no higher rate of chronic obstructive lung diseases observed with higher salt exposure (Lotz *et al*. 1998). The inverse relationship between salt exposure and ICAM-1 level, especially in smokers, may be explained by an increased respiratory clearing mechanism in smokers possibly leading to a loss of ICAM-1 expressing/secreting cells.

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References

ATTFIELD, M. D., TRABANT, G. D. and WHEELER, R. W. 1982, Exposure to diesel fumes and dust at six potash mines. *Annals of Occupational Hygiene*, **26**, (1–4), 817–831.

BECK, N. B., KOENIG, Q., LUCHTEL, D. L., ALTMAN, L. C., ORSBORN, M. T. and KENNEY, J. S. T. I. 1994, Ozone can increase the expression of intercellular adhesion molecule-1 and the synthesis of cytokines by human nasal epithelial cells. *Inhalation Toxicology*, **6**, 345–357.

BERNARD, C. and HERMANS, C. 1997, Biomonitoring of early effects on the kidney or the lung. *Science of a Total Environment*, **199**, 205–211.

BERNARD, A., LAUWERYS, R., NOEL, A., VANDELEENE, B. and LAMBERT, A. 1991, Determination of protein1 in normal and pathological urine. *Clinica Chimica Acta*, **201**, 231–246.

BERNARD, A., GONZALEZ- LORENZO, J. M. SILES, E., TRUJILLANO, G. and LAUWERYS, R. 1994, Early decrease of serum Clara cell protein in silica-exposed workers. *European Respiratory Journal*, **7**, 1932–1937.

BERNARD, A., MARCHANDISE, F. X., DEPELCHIN, S., LAUWERYS, R. and SIBILLE, Y. (1992a), Clara cell protein in serum and bronchoalveolar lavage. *European Respiratory Journal*, **5**, 1231–1238.

BERNARD, A., ROELS, H., BUCHET, J. P. and LAUWERYS, R. (1992b), Decrease of Clara cell protein in the serum in smokers (Letter). *Lancet*, **339**, 1620.

CANONICA, G. W., CIPRANDI, G., BUSCAGLIA, S., PESCE, G. and BAGNASCO, M. 1994, Adhesion molecules of allergic inflammation–recent insights into their functional roles. *Allergy*, **49**, 135–141.

CARELL, R. W. 1990, The molecular structure and pathology of alpha-1-Antitrypsin. *Lung*, **168** (Suppl.), 530–534.

DEVLIN, R. B., MCDONELL, W. F., MANN, R., BECKER, S., HOUSE, D. E., SCHREINEMACHERS, D. and KOREN, H. S. 1991, Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *American Journal of Respiratory Cell and Molecular Biology*, **4**, 72–81.

DI LORENZO, G., MANSUETO, P., MELLUSO, M., MORICI, G., NORRITO, F., CIGNA, D., CANDORE, G. and CARUSOM, C. 1995, Serum levels of soluble IL-2R, CD4 and CD8 in bronchial asthma. *Mediators of Inflammation*, **4**, 270–272.

DI STEFANO, A., MAESTRELLI, P., ROGGERI, A., TURATO, G., CALABRO, S., POTENA, A., MAPP, C. E., CIACCIA, A., COVACEV, L, FABBRI, M. and SAETTA, M. 1994, Upregulation of adhesion molecules in the bronchial mucosa of subjects with chronic obstructive bronchitis. *American Journal of Respiratory and Critical Care Medicine*, **149**, 803–810.

DIERYNCK, I., BERNARD, A., ROELS, H. and DE LEY, M. 1996, The human Clara cell protein: biochemical and biological characterisation of a natural immunosuppressor. *Multiple Sclerosis*, **1**, 385–387.

DODGE, D. E., RUCKER, R. B., PINKERTON, K. E., HASELTON, C. J. and PLOPPER, C. G. 1994, Dose-dependent tolerance to ozone. III. Elevation of intracellular Clara cell 10-kDa Protein in Central Acini of rats exposed for 20 months. *Toxicology and Applied Pharmacology*, **127**, 109–123.

GEARING, A. J. H., HEMINGWAY, I., PIGOTT, R., HUGHES, J., REES, A. J. and CASHMAN, S. J. 1992, Soluble forms of vascular adhesion molecules, E-selectin, ICAM-1, and VCAM-1. Pathological significance. *Annals of the New York Academy of Sciences*, **667**, 324–331.

GINNS, L. C., DE HOYOS, A., BROWN, M. C. and GAUMOND, B. R. 1990, Elevated concentration of soluble interleukin-2 receptors in serum of smokers and patients with lung cancer. *American Review of Respiratory Diseases*, **142**, 398–402.

GOSSET, P., TILLIELEBLOND, I., JANIN, A., MARQUETTE, C. H., COPIN, M. C., WALLAERT, B. and TONNEL, A. B. 1995, Expression of E-selectin, ICAM-1 and VCAM-1 on bronchial biopsies from allergic and non-allergic asthmatic patients. *International Archives of Allergy and Immunology*, **106**, 69–77.

GRAHAM, B. L., DOSMAN, J. A., COTTON, D. J. *et al*. 1984, Pulmonary function and respiratory symptoms in potash workers. *Journal of Occupational medicine*, **26**, 209–214.

GROTHEY, A., HEISTERMANN, P., PHILIPPOU, S. and VOIGTMANN, R. 1998, Serum levels of soluble intercellular adhesion molecule-1 (ICAM-1, CD54) in patients with non-small-cell lung cancer: correlation with histological expression of ICAM-1 and tumour stage. *British Journal of Cancer,* **77**, 801–807.

HAMACHER, J. and SCHABERT, T. 1994, Adhesion molecules in lung diseases. *Lung*, **172**, 189–213.

HIRATA, N., KOHROGI, H., IWAGOE, H., GOTO, E., HAMMAMOTO, J., FUJII, K., YAMAGUCHI, T., KAWANO, O. and ANDO, M. 1998, Allergen exposure induces the expression of endothelial

adhesion molecules in passively sensitized human bronchus: time course and the role of cytokines. *American Journal of Respiratory Cell and Molecular Biology*, **18**, 12–20.

HOHBEIN, K. 1989, Chronische unspezifische Atemtrakterkrankungen bei Kalibergleuten der DDR in Beziehung *zur Exposition durch Spreng-* und Kraftfahrzeugabgase sowie Kalisalzstaub. Diss., Akad. für Ärztl. Fortb. Berlin.

HONG, Z. 1996, Serum Clara cell protein (CC-16), a new valid marker of the distal airway damages caused by air pollutants in rats. *Journal of Tongji Medical University*, **16**, 223–228.

ISHII, Y. and KITAMURA, S. 1995, Elevated levels of soluble ICAM-1 in serum and BAL fluid in patients with active sarcoidosis. *Chest*, **107**, 1636–1640.

KATO, M., HATTORI, T., KITAMURA, M., BEPPU, R., YANAGITA, N. and NAKASHIMA, I. 1995, Soluble ICAM-1 as a regulator of nasal allergic reaction under natural allergen provocation. *Clinical and Experimental Allergy*, **25**, 744–748.

KOBAYASHI, T., HASHIMOTO, S., IMAI, K., AMEMIYA, E., YAMAGUCHI, M., YACHI, A. and HORIE, T. 1994, Elevation of serum soluble intercellular adhesion molecule-1 (sICAM-1) and E-selectin levels in bronchial asthma. *Clinical and Experimental Immunology*, **96**, 110–115.

LESUR, O., BERNARD, A., ARSALANE, K., LAUWERYS, R., BEGIN, R., CANTIN, A. and LANE, D. 1995, Clara cell protein (CC-16) induces a phospholipase A(2)-mediated inhibition of fibroblast migration *in vitro*. *American Journal of Respiratory and Critical Care Medicine*, **152**, 290–297.

LESUR, O., BERNARD, A. M. and BEGIN, R. O. 1996, Clara cell protein (CC-16) and surfactant-associated protein A (SP-A) in asbestos-exposed workers. *Chest*, **109**, 467–474.

LOTZ, G., GIERKE, E., KERSTEN, N., SÄVERIN, R., SCHNEIDER, W. D., THÜRMER, H. and TITTELBACH, U. 1997, Exposure response relationships between occupational exposure to potash and lung function in salt miners. Abstracts, ERS Annual Congress, Berlin, 20–24. Sept. 1997. *European Respiratory Journal*, **10** (Suppl. 25), 232.

LOTZ, G., BACKÉ, E., GIERKE, E., KERSTEN, N., SÄVERIN, R., SCHNEIDER, W. D., THÜRMER, H. and TITTELBACH, U. 1998, Zur Wirkung von Salzstäuben auf das Atmungssystem (Abschlußbericht). *Schriftenreihe der Bundensanstalt für Arbeitsschutz und Arbeitsmedizin*. Fb 791, Dortmund/Berlin.

MARKHAM, J. W. and TAN, L. K.-T. 1981, Concentrations and health effects of potash dust. *American Industrial Hygiene Association Journal*, **42**, 671–674.

MASSARO, G. D. 1987, The Clara cell: secretory and developmental studies in the rat. *European Journal of Respiratory Diseases*, **71** (Suppl.), 52–58.

MATSUMOTO, K., TAKI, F., MIURA, M., MATSUZAKI, M. and TAKAGI, K. 1994, Serum levels of soluble IL-2R, IL-4, and soluble FcεRII in adult bronchial asthma. *Chest*, **105**, 681–686.

MONTEFORT, S., LAI, C. K. W., KAPAHI, P., LEUNG, J., LAI, K. N., CHAN, H. S., HASKARD, D. O., HOWARTH, P. H. and HOLGATE, S. T. 1994, Circulating adhesion molecules in asthma. *American Journal of Respiratory and Critical Care Medicine*, **149**, 1149–1152.

NEUHANN, H. F., STILLER-WINKLER, R. and MALIN, E. 1994, Die Konzentration von Alpha-1-PI im Serum 55-jähriger Frauen aus Regionen mit unterschiedlicher Luftbelastung in NRW. *Zentralblatt für Hygiene und Umweltmedizin*, **195**, 463–469.

POSSNER, W. 1967, Untersuchungen zur Bronchitisprävalenz und Häufigkeit von Ventilationsstörungen bei Kaliarbeitern. F/E Arbeitsmedizin im Kalibergbau, Bericht F/E-Nr. 4520167/7003/67 VE Kombinat Kali.

REGENSPURGER, G. 1966, Lungenfunktionsdiagnostische Untersuchungen zur Frage der Belastung der Atmungsorgane durch das Untertagemilieu im Kalibergbau. Diss., Med. Akad. Erfurt. pp. 1–71.

RIISE, G. C., LARSSON, S., LOFDAHL, C. G. and ANDERSSON, B. A. 1994, Circulating cell adhesion molecules in bronchial lavage and serum in COPD patients with chronic bronchitis. *European Respiratory Journal*, **7**, 1673–1677.

RUBIN, A. and NELSON, D. L. 1990, The soluble interleukin-2 receptor: biology, function, and clinical application. *Annals of Internal Medicine*, **113**, 619–627.

SCHABERG, T., RAU, M., OERTER, R., LIEBERS, U., RAHN, W., KAISER, D., WITT, C. and LODE, H. 1996, Expression of adhesion molecules in peripheral pulmonary vessels from smokers and nonsmokers. *Lung*, **174**, 71–81.

SHIJUBO, N., ITOH, Y., YAMAGUCHE, T., SHIBUYA, Y., MORITA, Y., HIRASAWA, M., OKUTANI, R., KAWAI, T. and ABE, S. 1997, Serum and BAL Clara cell 19 kDa protein (CC10) levels and CC10-positive bronchiolar cells are decreased in smokers. *European Respiratory Journal*, **10**, 1108–1114.

SPLETTSTÖSSER, G., SCHÖNEICH, R. and SCHNEIDER, W. D. 1990, Zur Wirkung des Tabakrauches auf immunologische Parameter. *Zeitschrift für die gesamte Hygiene*, **36**, 649–651.

STEERENBERG, P. A., ZONNENBERG, J. A. J., DORMANS, J. A. M. A., JOON, P. N. T., WOUTERS, I. M., VAN BREE, L., SCHEEPERS, P. T. J. and LOVEREN, H. V. 1998, Diesel exhaust particles induced release of interleukin 6 and 8 by (primed) human bronchial epithelial cells (BEAS 2B) *in vitro*. *Experimental Lung Research*, **24** (1), 85–100.

STILLER,-WINKLER, R., IDEL, H., G., SPIX, C. and DOLGNER, R. 1996, Influence of air pollution on humoral immune response. *Journal of Clinical Epidemiology*, **49**, 527–534.

TAKAHASHI, N., LIU, M. C., PROUD, D., YU, X. Y., HASEGAWA, S. and SPANNHAKE, E. W. 1994, Soluble intracellular adhesion molecule 1 in bronchoalveolar lavage fluid of allergic subjects following

segmental antigen challenge. *American Journal of Respiratory and Critical Care Medicine*, **150**, 704–709.

TAKAHASHI, N., YU, X. Y., SCHOFIELD, B. H., KLEEBERGER, S. R., SCOTT, A. L., HASEGAWA, S. and SPANNHAKE, E. W. 1995, Expression of ICAM-1 in airway epithelium after acute ozone exposure in the mouse. *Journal of Applied Physiology*, **79**, 1753–1761.

TOLLERUD, D. J., KURMAN, C. C., NELSON, D. L., BROWN, L. M., MALONEY, E. M. and BLATTNER, W. A. 1994, Racial variation in serum-soluble interleukin-2 receptor levels–a population-based study of healthy smokers and nonsmokers. *Clinical Immunology and Immunopathology*, **70**, 274–279.

TURATO, G., DI STEFANO, A., MAESTRELLI, P., MAPP, C. E., RUGGIERI, M. P., ROGGERI, A., FABBRI, L. M. and SAETTA, M. 1995, Effect of smoking cessation on airway inflammation in chronic bronchitis. *American Journal of Respiratory and Critical Care Medicine*, **152**, 1262–1267.

VIRCHOW, J. C., WALKER, C., HAFNER, D., KORTSIK, C., WERNER, P., MATTHYS, H. and KROEGEL, C. 1995, T cell and cytokines in bronchoalveolar lavage fluid after segmental allergen provocation in atopic asthma. *American Journal of Respiratory and Critical Care Medicine*, **151**, 960–968.

YANG, H. M., MA, J. Y. C., CASTRANOVA, V. and MA, J. K. H. 1997, Effects of diesel exhaust particles on the release of interleukin-1 and tumor necrosis factor-alpha from rat alveolar macrophages. *Experimental Lung Research*, **23**, (3), 269–284.

ZANGRILLI, J. G., SHAVER, J. R., CIRELLI, R. A., CHO, S. K., GARLISI, C. G., FALCONE, A., CUSS, F. M., FISH, J. E. and PETERS, S. P. 1995, sVCAM-1 levels after segmental antigen challenge correlate with eosinophil influx, IL-4 and IL-5 production and the late phase response. *American Journal of Respiratory and Critical Care Medicine*, **151**, 1346–1353.