# COMPARATIVE INHALATION HAZARDS OF TITANIUM DIOXIDE, SYNTHETIC AND NATURAL GRAPHITE

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Occupational exposure to airborne graphite may occur in manufacturing and application processes. Synthetic graphite (SG) is a pure crystalline form of carbon from high temperature treatment of petroleum products, contains less than 1% quartz and is regarded as a "nuisance" dust (ACGIH TLVs®). Natural graphite (NG) is the mineral form of graphitic carbon and contains associated silicate minerals. A series of inhalation studies were conducted to study the effects of crystalline silica on graphite pneumoconiosis; titanium dioxide ($TiO_2$) was used as a negative control. Fischer 344 rats were exposed by inhalation to 100 mg/m$^3$ SG, NG and $TiO_2$ for 4 hrs/day for 4 days. At 24 hrs and 14 days post-exposure (PE), exposed and air control rats were evaluated for bronchoalveolar lavage (BAL), physiological, pathological changes. Previous acute inhalation studies with crystalline silica resulted in persistent BAL changes correlated with adverse histopathology. BAL analysis detects differences between "nuisance" dusts and silica. Inhalation of NG containing 1–2% crystalline silica resulted in reversible BAL effects similar to other "nuisance" dusts (SG, $TiO_2$). Impairment of lung clearance from high dust burdens with greater silica content may be the causitive factor in graphite pneumoconiosis. (Supported by the U.S. Army Biomedical Research Development Laboratory.)

## INTRODUCTION

Synthetic and/or natural graphite dust may have military applications which could result in inhalation hazards. CRDEC has tested synthetic (Asbury Micro 260) and natural (Asbury Micro 650) graphites and found that acute inhalation exposure in Fischer 344 rats resulted in a mild reversible inflammatory response at high concentrations (500 mg/m$^3$) for the synthetic material.[21]) A repeated inhalation study with the synthetic graphite also showed more changes at a lower concentration (100 mg/m$^3$) reversible at 3 months post-exposure (PE).[22] The purpose of this study was to compare the toxicity of natural and synthetic graphite using titanium dioxide as a negative control. Both synthetic graphite and titanium dioxide are classifed as "nuisance dusts" as defined by ACGIH.[3] Purported "nuisance" dusts have a history of little adverse effect and do not produce significant organic disease or toxic effect when exposures are kept under control. A Threshold Limit Value (TLV) of 10 mg/m$^3$ of total dust (less than 1% quartz) is recommended for "nuisance" dusts for a normal workday. For materials containing more than 1% quartz, the environment should be evaluated against the TLV of 0.1 mg/m$^3$ for respirable quartz. The natural graphite used in this study contains 1.85% silica and chemically may not meet the nuisance dust requirement; however, this material may behave biologically like other nuisance dusts (synthetic graphite and titanium dioxide). According to the ACGIH, the biological criteria of a nuisance dust is defined by the following lung tissue reaction: 1) the architecture of the air spaces remains intact; 2) collagen (scar tissue) is not formed to a significant extent; and 3) the tissue reaction is potentially reversible. In addition to these histopathological indicators of toxicity, pulmonary function and bronchoalveolar lavage (BAL) were used to compare the toxicity of these graphite dusts to titanium dioxide.

## MATERIALS AND METHODS

### Experimental Design and Test Materials

Groups of 20 male Fischer 344 rats (CDF/Crl BR), commercially procured from Charles River Laboratories, were exposed by whole body inhalation to 100 mg/m$^3$ of each test material on four consecutive days, four hours/day. At 24 hrs and 14 days PE, exposed and air control rats were evaluated for BAL, physiological and pathological changes. Toxic observations were recorded daily and weights were taken at weekly intervals.

The synthetic graphite used in this study is Asbur Micro 260 (less than 1% silica) and the natural graphite is Asbur Micro 650 (1.85% silica). The titanium dioxide was a gift from NL Chemicals Inc. and is a high purity rutile form of titanium dioxide. All three test materials contained negligible amounts of contaminants.

### Chamber Operation

The Hazelton 2000 liter stainless steel inhalation chambers were used for this study. A unique feature of the chamber is the multi-tier arrangement of the cage units and catch pans which facilitates good mixing within the chamber and helps promote a nearly uniform aerosol concentration throughout the chamber.[12] This uniformity has been verified by both fixed point aerosol sampling measurements, residence time distribution measurements, and flow visualization studies.[2,13] Four Hazelton 2000 liter chambers were set up as shown in Figure 1 under climate controlled conditions (temperature = 74° ± 4°; relative humidity = 40% ± 10%). All four chambers were manifolded to a single blower unit which pulls air from the surrounding room through each of the chambers; all air was filtered prior to being exhausted

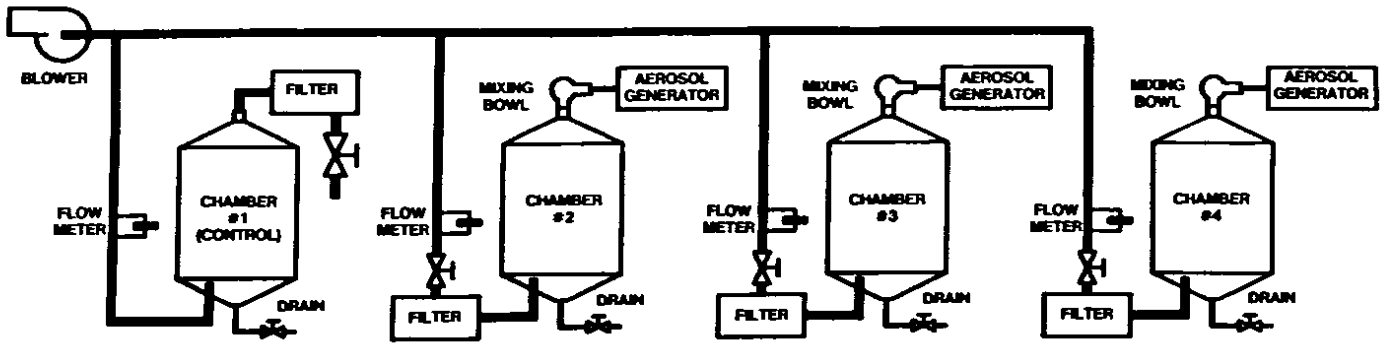


Figure 1. Exposure facility.

outside. The inlet ports to the exposure chambers were each fitted with 15 liter glass mixing bowls to aid in aerosol dispersal and the control chamber and was fitted with a particulate filter on its input in place of a mixing bowl. Each chamber exhaust line has an orifice meter downstream of the particulate filter for the purpose of monitoring chamber flow. Gate valves provided on each chamber enable course flow regulation.

The aerosol generation system for titanium dioxide consisted of an AccuRate series 300 screw feeder and attached vibration device which metered the dust at a uniform rate to a Jet-O-Mizer aerosol mill depicted in Figure 2. The aerosol mill was equipped with air jets supplied with compressed air at 55 psig. High velocity air emanating from the jets resulted in high particle to particle shear forces which readily caused the break up of agglomerates. Consequently, a relatively highly dispersed aerosol was produced at the outlet of the aerosol mill.

The AccuRate series 300 feeders were also used to deliver the graphites to the dust generators. Dispersion of the graphite dusts was accomplished using a Metronics aerosol generator depicted in Figure 3. This device is in essence a centrifugal blower with a deep bladed impellor. Feed material falls into the center of the impellor and is driven against the blades by centrifugal force resulting in particle deagglomeration and dispersion. The resultant aerosol was fed directly into the chamber mixing bowl. The appropriate blower speed was determined during the calibration phase and was regulated by means of a variance.

Prior to the start of exposures, calibration of the chamber was conducted to assure a stable concentration. The aerodynamic particle size of each test material was determined using a Sierra® Instruments cascade impactor (Model 2210-K, 10 stage). The mass median aerodynamic diameter (MMAD) and geometric standard deviation ($\sigma_g$) of each test material were determined during the calibration and exposure phases of the study. The MMAD in micrometers and the ($\sigma_g$) were 2.38 (2.61) for natural graphite, 2.27 (2.57) for synthetic graphite, and 1.50 (2.25) for titanium dioxide.

The average concentrations for the four days of exposure for each test material were: 102.1 mg/m$^3$, natural graphite; 100.4 mg/m$^3$, synthetic graphite; and 101.5 mg/m$^3$, titanium dioxide. The overall coefficient of variation for concentration was less than 15 percent.

### Biological Evaluations and Data Analysis

Lung lavage and pulmonary physiological testing were performed on the same animal to enable correlation of biochemical changes with functional changes. The details of the physiological evaluations and BAL analyses were previously described by Thomson et al.[18] Macrophage concentration was determined in a hemocytometer and cell viability was conducted via the trypan blue exclusion test.[7]

At 24 hours and 14 days PE, the test and control rats identified for pathological evaluation were killed using carbon dioxide gas and complete necropsies were performed by Pathology Associates Inc., Ijamsville, Md. All tissues were fixed in 10% neutral buffered formalin, trimmed, dehydrated, embedded in paraffin, sectioned at 6 *m and stained with hematoxylin and eosin. Representative sections were examined for all test groups and controls.

Data analysis was conducted according to a statistical "decision tree" as described by Gad and Weil.[5] First, Bartletts' Test for homogenicity of variance was used as a check of the assumption of equivalent variances, followed by the use of ANOVA (analysis of variances). Non-parametric, heterogeneous data was analyzed by the Kruskal-Wallis nonparametric ANOVA. Finally, Dunnett's Test was used on parametric homogeneous data to identify significantly different groups.

## RESULTS

### Physiological and Bronchoalveolar Response

Throughout the entire study, the control and test animals gained weight at the same rate; there were no statistically significant differences between the groups. There were no adverse toxic signs exhibited by the animals, normal activity occurred pre and post exposure. The graphite exposed rats were charcoal colored following exposure and remained "dirty" looking throughout the 14 day post exposure period despite some preening. The pulmonary physiological evaluation of the rats exposed to titanium dioxide and graphite dusts

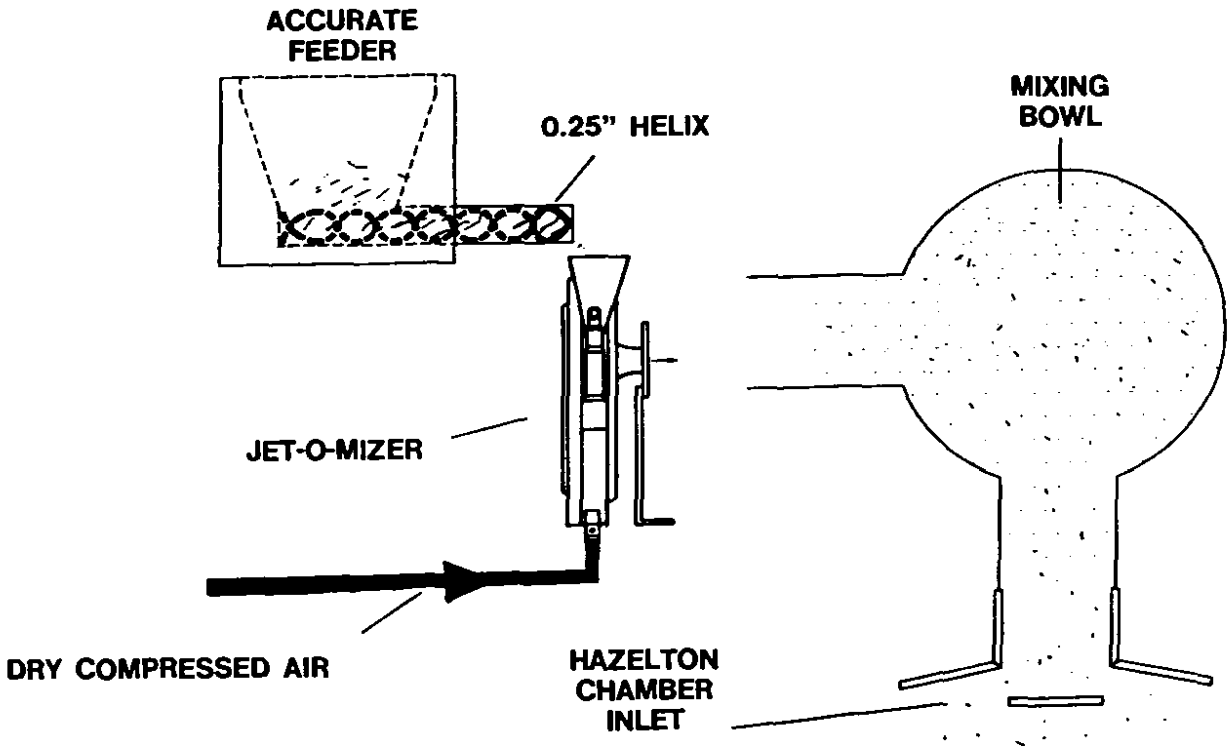


Figure 2. $TiO_2$ aerosol generation system.

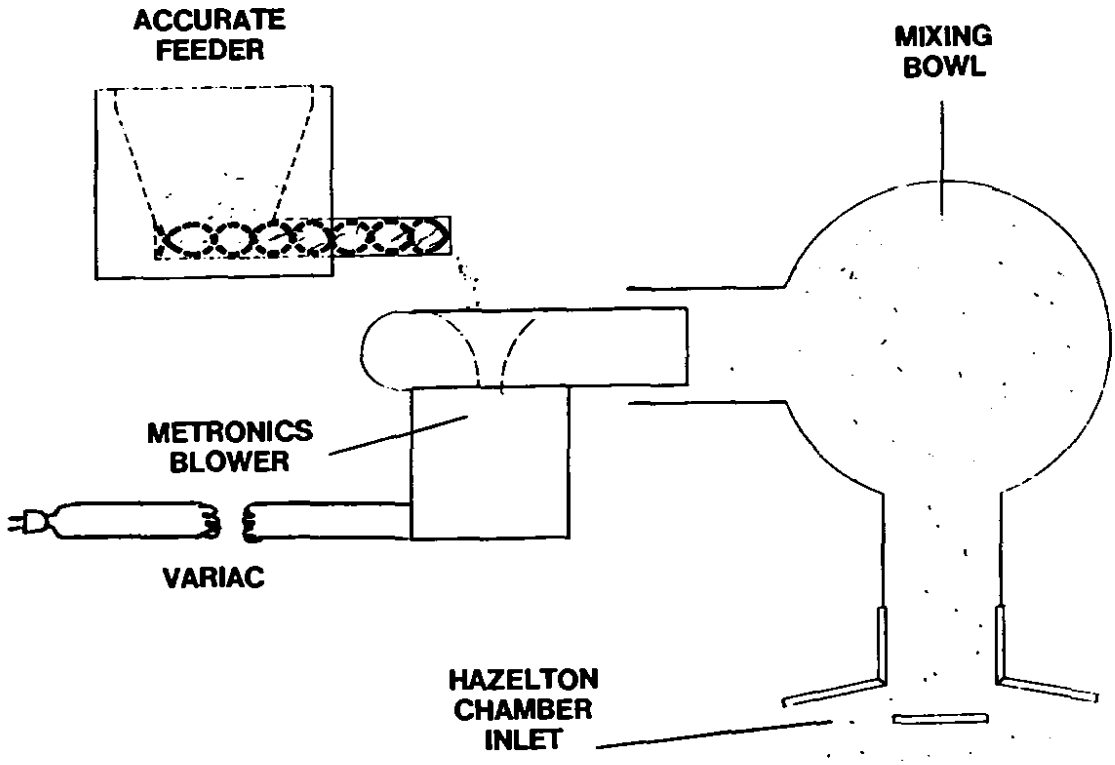


Figure 3. Graphite aerosol generation system.

showed an apparent statistically significant decrease in pulmonary resistance at 24 hours PE in the rats exposed to synthetic graphite and a significant increase in respirator rate at 14 days PE in the rats exposed to titanium dioxide. Neither of these apparent changes has any biological significance. Previous acute and repeated inhalation studies on synthetic graphite did not result in any consistent significant changes in pulmonary resistance.[21,22]

The enzymatic and protein analyses of the lavage fluid are summarized in Figure 4. There were significant increases in protein at 24 hours PE with all three dusts but at 14 days all values were within control levels. At 24 hours PE, there were significant increases in β-Glu and ALKP for both graphite dusts and an increase in LDH for the natural graphite. There was an unexplainable decrease in ALKP for titanium dioxide which may be caused by a material interference with the assay; this effect is being investigated. By 14 days PE, all enzymatic changes were resolved.

Cytological analyses of the lavage fluid are listed in Table I. All three dusts exhibited an influx of polymorphonuclear neutrophils (PMN) at 24 hours PE but the graphite dusts elicited a greater PMN response. Likewise, natural graphite exposure resulted in the largest increase in total cells. By 14 days PE, the PMN response had diminished to almost control levels. There was no decrease in macrophage viability from exposure to any of the test materials.

### Pathological Evaluations

The gross observations noted at the time of necropsy indicated that several of the graphite exposed rats had discolored or mottled lungs. There were no apparent differences in body or organ weights. Treatment related changes were present in the lungs of all exposed rats consisting of brown to black, isotropic pigment. At 24 hours PE in all cases, the pigment was present either free or within macrophages in terminal airways and alveoli. Microscopically, the three types of pigment were indistinguishable from each other. There was no pigment in the peribronchial lymph nodes and no adverse tissue reaction to it. By 14 days PE, there was no free pigment (extracellular) in the lungs of the exposed rats. Again, the three types of pigment were indistinguishable; however, in the graphite exposed rats, the pigment-laden macrophages tended to be aggregated in small groups more than in the titanium dioxide exposed rats. The only other changes were two minimal foci of epithelial hyperplasia in the alveoli and/or the terminal bronchioles of three rats exposed to synthetic graphite and one rat exposed to titanium dioxide. The pigmented macrophages were not associated with the hyperplasia. It was concluded that the degree of pigmentation was mild in all exposed rats and nearly identical within and between groups.

## DISCUSSION

Inhalation exposure of Fischer 344 male rats to 100 mg/m$^3$ of titanium dioxide, natural and synthetic graphite dusts for 4 hrs/day for four days resulted in minimal adverse effects. There were no adverse toxic signs following exposure, no mortality and no consistent pulmonary function changes. All the rats gained weight at the same rate as the controls. BAL analyses resulted in increases in protein for all three materials; increases in β-Glu and ALKP for both graphites; and increases in LDH for natural graphite at 24 hours PE. The increase in LDH is reported to be indicative of damage to the pulmonary Type 1 cells while ALKP increases may be correlated with Type II cell hyperplasia.[8] Type II cell hyperplasia was only observed in three rats at 14 day PE, two from the synthetic graphite exposed group and one from the titanium dioxide exposed group. This effect was observed in a previous study where rats were exposed to 100 mg/m$^3$, 2 hours/day, 5 days/wk for two weeks.[22] Perhaps a longer repeated exposure would have resulted in more Type II cell hyperplasia in this study. Since Type II cells are the progenitors of Type I cells,[4] this would be an indicator that the damaged alveolar epithelium is undergoing repair and replacement. The graphite exposed rats also had increases in β-Glu which is a lysosomal enzyme released by phagocytic cells in response to inflammation.[8] These enzymatic changes correlate with the BAL cytological profile (i.e., increases in PMN and total nucleated cells), which are indicative of an inflammator response. By 14 days PE, all BAL alterations were resolved.

The histopathological evaluation revealed mild lung pigmentation in all the exposed rats with more aggregates of pigment in the graphite exposed rats at 14 days PE. The macrophages seen in the alveoli appear to be actively phagocytizing all three materials. There was no decrement in macrophage viability which is in agreement with previous studies with synthetic graphite and titanium dioxide.[1] No pigment was observed in the peribronchial lymph nodes; this was expected since in prior inhalation studies with graphite, pigmentation in the lymph nodes was not evident until 3 months PE. Clearance of these dusts may be a slow, protracted process.

The BAL changes seen after repeated exposure to graphite were more severe than the changes following a single exposure. Previous acute inhalation exposure to graphite resulted in minimal cytological changes reversible by 14 days PE and no enzymatic BAL changes.[21] However, the BAL response in this study is mild compared to the dramatic inflammatory reactions observed in acute studies with brass powder,[18] and is not as persistent as the effects seen with aluminum

single 100 mg/m$^3$ inhalation exposure to quartz, BAL enzymes were elevated two to five hundred percent over controls at 3 days and 3 months PE. The changes with graphite were minimal and reversible.

The repeated inhalation studies in this report and the previous acute inhalation exposure to synthetic graphite even at very high concentrations (500 mg/m$^3$ does not result in any permanent effects. This is in agreement with the OSHA[14] and Documentation of TLVs[3] guidelines which regard synthetic graphite as a nuisance dust. The higher quartz content (>1%) of natural graphite supposedly accounts for the greater risk of developing fibrosis; thus, natural graphite is assigned a TLV of 2.5 mg/m$^3$. However, this hypothesis is not conclusive; a survey of the literature on the etiology of coalworkers' pneumoconiosis (CWP) reveals uncertainty as to what part quartz plays in pathogenesis.[15] Several studies in animals have implicated quartz as the causative factor in

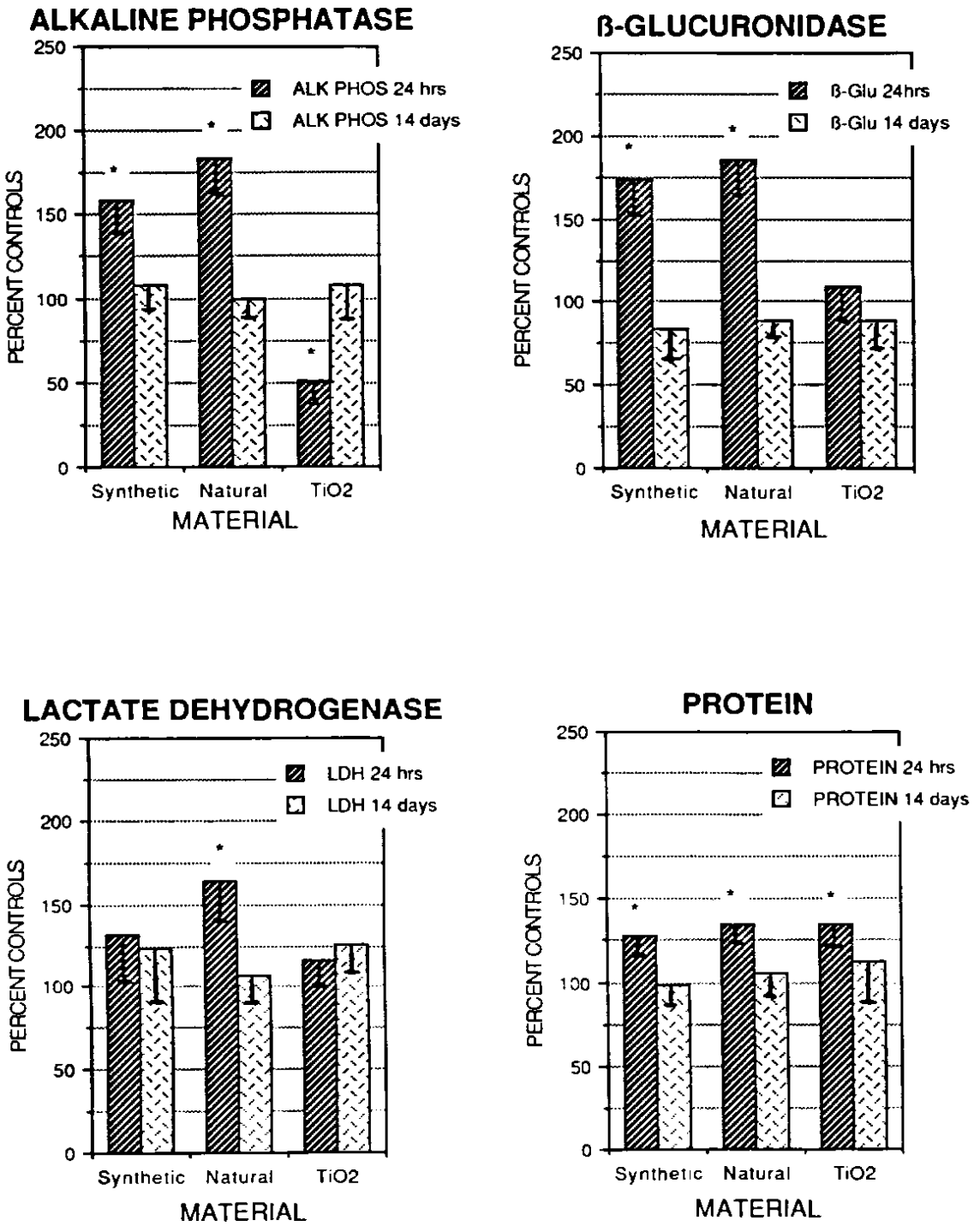


Figure 4. BAL results for graphite and $TiO_2$ exposed rats.

Table I
Cytological Analysis of Bronchoalveolar Lavage Fluid

| | | WBC x10$^3$ | TOTAL x10$^4$ | VIABILITY % | MACROPHAGE % | LYMPH % | PMNS % |
|---|---|---|---|---|---|---|---|
| **24 Hours Post Exposure** | | | | | | | |
| CONTROL | x | 2.22 | 4.34 | 97 | 98 | 2 | 0 |
| | s | 0.50 | 1.51 | | 2 | 1 | 0 |
| SYNTHETIC | x | 2.40 | 5.18 | 95 | 56 | 1 | 43 |
| | s | 0.46 | 0.89 | | 7 | 0 | 7 |
| NATURAL | x | 3.37* | 6.10 | 94 | 46 | 2 | 52 |
| | s | 0.73 | 1.26 | | 10 | 1 | 10 |
| TITANIUM OXIDE | x | 1.45 | 6.22 | 96 | 85 | 4 | 11 |
| | s | 1.20 | 2.07 | | 15 | 5 | 11 |
| **14 Days Post Exposure** | | | | | | | |
| CONTROL | x | 2.00 | 4.41 | 98 | 97 | 2 | 1 |
| | s | 0.66 | 1.11 | | 2 | 1 | 1 |
| SYNTHETIC | x | 2.13 | 5.29 | 98 | 92 | 3 | 5 |
| | s | 0.43 | 1.01 | | 7 | 3 | 4 |
| NATURAL | x | 2.58 | 6.12* | 99 | 92 | 2 | 6 |
| | s | 0.57 | 0.61 | | 4 | 1 | 4 |
| TITANIUM OXIDE | x | 1.88 | 3.67 | 98 | 94 | 2 | 4 |
| | s | 0.42 | 0.53 | | 3 | 2 | 3 |

* significant p=0.05 (t-test)

mixed dust fibrogenesis. Martin et al.[11] found collagen formation after 18 months in the lungs of rats that had inhaled a coal mixture with 5% quartz for 80 days. At concentrations above 10% quartz, the formation of fibrotic nodules and collagen occurred at a rate five times higher than coal alone. Further confirmation of this theory was demonstrated by Schlipkoter et al.[18] in experiments where quartz, coal and titanium dioxide, alone and in mixtures, were administered to rats intraperitoneally. Fibrosis was induced when quartz was added to the mixtures and the authors concluded that whenever quartz is present in a particular mine dust producing CWP, it should be considered the dangerous agent. This interpretation according to Parkes[15] is contradicted by a number of observations in human beings. Both simple pneumoconiosis (benign dusty lung) and progressive massive fibrosis have occurred in men exposed to artificial or quartz-free graphite.[6,16,17] In each caae, quartz was absent or less than 1% in the lungs; therefore, such instances imply quartz is not the pathogenic factor. The controversy is more than an academic debate since occupational exposure standards are based upon the quartz content of the dust in question (eg. graphite). Recent epidemiological studies in British mines showed that an apparent increase in the prevalence of pneumoconiosis with increasing quartz exposure is reversed in the presence of high clay mineral exposure (aluminum silicate clays are known to inhibit silicosis) and that mass concentration of respirable dust is the best exposure index when the quartz content does not exceed 7.5%.[15] This "mass" effect of dust exposure has been recently demonstrated by the results of chronic inhalation studies conducted with titanium dioxide. Lee et al.[10] found fibrosis and bronchoalveolar adenomas in the lungs of rats exposed to 250 mg/m$^3$ of titanium dioxide for 6 hrs/day, 5 days/wk, for 2 years. The pulmonary lesions were the result of overwhelming the lung clearance mechanisms.

## CONCLUSIONS

Repeated inhalation exposure of Fischer 344 rats to 100 mg/m$^3$ of titanium dioxide, natural graphite, and synthetic graphite for 4 hours/day for four days resulted in a mild inflammatory response 24 hours PE. BAL changes were the most sensitive indicator of damage; although the enzymatic and cytological alterations were evident with all three materials, there were greater increases with the graphite dusts. Even though the graphite dusts and titanium dioxide were still present in the alveolar macrophages of each respective group of rats, by 14 days PE, all BAL changes were resolved. This seems to indicate that the initial period of inflammation had ceased and a slow clearance was in process. There appears to be no deleterious tissue reaction to any of the materials at the levels tested in this study.

In this experiment, synthetic graphite, natural graphite, and titanium dioxide meet the criteria of the ACGIH for a nuisance dust: (1) the architecture of the air spaces remained intact; (2) collagen (scar tissue) was not formed; and (3) the tissue reaction was potentially reversible. Repeated exposure to graphite dust results in more pulmonary damage than single exposures. If the nuisance dust TLV (10 mg/m$^3$) is exceeded, respirator protection should be utilized.

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# II


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