Human Pulmonary Responses to Experimental Inhalation of High Concentration Fine and Ultrafine Magnesium Oxide Particles

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Exposure to air polluted with particles less than 2.5 µm in size is associated epidemiologically with adverse cardiopulmonary health consequences in humans. The goal of this study was to characterize human pulmonary responses to controlled experimental high-dose exposure to fine and ultrafine magnesium oxide particles. We quantified bronchoalveolar lavage (BAL) cell and cytokine concentrations, pulmonary function, and peripheral blood neutrophil concentrations in six healthy volunteers 18 to 20 hr after inhalation of fine and ultrafine magnesium oxide particles produced from a furnace system model. We compared postexposure studies with control studies from the same six subjects. Mean ± standard deviation (SD) cumulative magnesium dose was 4,138 ± 2,163 min × mg/m^3. By weight, 28% of fume particles were ultrafine (<0.1 µm in diameter) and over 98% of fume particles were fine (<2.5 µm in diameter). There were no significant differences in BAL inflammatory cell concentrations, BAL interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor, pulmonary function, or peripheral blood neutrophil concentrations postexposure compared with control. Our findings suggest that high-dose fine and ultrafine magnesium oxide particle exposure does not produce a measurable pulmonary inflammatory response. These findings are in marked contrast with the well-described pulmonary inflammatory response following zinc oxide particle inhalation. We conclude that fine and ultrafine particle inhalation does not result in toxicity in a generic manner independent of particle composition. Our findings support the concept that particle chemical composition, in addition to particle size, is an important determinant of respiratory effects. *Key words*: BAL, bronchoalveolar lavage, cytokines, fine particles, inhalation, magnesium, occupational, pulmonary function, ultrafine particles.
Environ Health Perspect 105:1234–1237 (1997). *http//ehis.niehs.nih.gov*

Fine and ultrafine particulate air pollution appears to be associated with important adverse health consequences. A number of observational population-based epidemiologic studies indicate a strong relationship between mortality and ambient air pollution from particulates less than 2.5 µm in size (*1–9*). Animal studies of fine and ultrafine particulate matter, including experimental studies with concentrated ambient air samples, have found these exposures to be acutely toxic, supporting the epidemiologic association in humans (*10–12*). Despite this strong evidence linking fine and ultrafine particle inhalation with adverse health effects, the mechanisms by which particle toxicity may be exerted are poorly understood. Indeed, the extent to which particle chemical composition itself determines toxicity, as opposed to size and other generic physical characteristics of particulates, remains unclear. To date there has been no controlled human experimental exposure model of fine and ultrafine particle inhalation effects.

Metal oxides comprise an important group of particulate pollutants. For example, zinc, magnesium, iron, and vanadium oxides are components of fly ash, a product of fossil fuel combustion. Exposure to fly ash, which occurs in a variety of occupational and environmental settings, has been linked with lung function decline including obstructive lung disease (*13*) and interstitial fibrosis (*14*). Further, inhalation of zinc oxide fume in high concentration is a well-established cause of the occupational flulike syndrome metal fume fever (*15–17*). We have previously reported a pulmonary inflammatory cellular response in healthy humans following experimental inhalational exposure to zinc oxide fume (*18–20*).

To determine whether this represents a specific chemical effect of zinc oxide or rather a potentially generic response to fine and ultrafine metal oxide particles, we carried out a series of experimental human exposures to purified magnesium oxide fume. The principal goal of this investigation was to determine whether magnesium oxide inhalation invokes a similar response to the inflammatory cellular influx we have observed following zinc oxide fume exposure. We hypothesized that absence of such a response, despite a high fume exposure level, would argue against a generic particulate response driven solely by particulate size and number of particles per milligram inhaled.

Material and Methods

Study design overview. We exposed six normal volunteer subjects to inhaled purified magnesium oxide particles. We produced metal oxide fume with a furnace system under controlled conditions and quantified cumulative magnesium oxide dose for each exposure. We assessed particle size and particle shape by cascade impactor analysis and scanning electron microscopy. We analyzed pulmonary inflammatory cell and cytokine responses 20 hr postexposure by analysis of bronchoalveolar lavage (BAL) fluid and we compared these findings with paired control BAL samples in the same six subjects obtained without prior magnesium oxide exposure. We also compared peripheral blood neutrophil and pulmonary function 18 hr postexposure with baseline values. The investigation was approved by the University of California, San Francisco, Committee on Human Research.

Study subjects. The age, sex, and smoking status for each of the six study subjects are presented in Table 1; we studied both smokers and nonsmokers. None of the volunteers had any history of occupational exposure to magnesium oxide and none reported any history of chronic or acute lung disease.

Magnesium oxide fume exposure. We produced controlled quantities of freshly generated purified magnesium oxide fume utilizing a furnace system design originally developed by McCarthy and colleagues (*21*), which we later used in human zinc oxide studies (*20*). We assessed fume particle size by cascade impactor analysis. We used a micro-orifice uniform deposit impactor (MOUDI), model no. 110, with an operation flow rate of 30 l/min (MSP Corporation, Minneapolis, MN). The MOUDI cut points were inlet cut point, 18

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The authors thank Homer Boushey for assistance with bronchoscopy and Jane Liu for assistance with the BAL protein assay.
Supported in part by National Research Service Award No. HL07185 and a Foundation for Occupational Health and Research Award (W.G.K.), and Research Career Development Award No. HL03225 (P.D.B.).
Received 27 December 1996; accepted 26 August 1997.

µm; stages 1–10 (in µm), 10, 5.6, 3.2, 1.8, 1.0, 0.56, 0.32, 0.18, 0.1, 0.056. As shown in Figure 1, by weight, over 98% of fume particles were fine or ultrafine and 98.6% were less than 1.8 µm in diameter. The greatest percentage (42.0%) of particles by weight were between 0.1 and 0.18 µm in diameter; 28.6% of particles were ultrafine (<0.1 µm in diameter). The total concentration during particle size sampling was 90.6 mg/m^3. Also shown in Figure 1, for comparison, is the particle size distribution for zinc oxide particles generated by the same furnace system and used in a previously published experimental inhalation investigation (*20*). Fume particles are shown in the scanning electron micrograph (Fig. 2).

We quantified magnesium concentration for each experimental exposure by sampling a known volume filtered through a cellulose acetate membrane (0.22 µm pore), which was analyzed for metallic magnesium by inductively coupled plasma atomic emission (D & M Laboratories, Petaluma, CA, and Data Chem Laboratories, Cincinnati, OH). We carried out exposures over a range of magnesium oxide concentrations (Table 2). The median magnesium concentration (range) was 133.0 mg/m^3 (5.8–230.0 mg/m^3). We varied exposure time in order to produce a range of cumulative exposures; exposure duration was determined prior to exposure. We calculated cumulative exposure levels as the cross-product of the concentration of magnesium oxide, measured as metallic magnesium in milligrams per cubic meter, times the duration of the inhalation exposure expressed in minutes (min × mg/m^3). Cumulative magnesium exposure (Table 2) ranged from 261 to 6,435 min × mg/m^3. Subjects inhaled magnesium oxide fume with medical-grade air through a mouth-breathing face mask. All subjects completed an exposure in full without discomfort or difficulty. Subjects were asked to record their body temperature during the evening following the afternoon exposure and to document any symptoms including flulike symptoms of myalgias, fatigue, and rigors.

Pulmonary function testing. Baseline (preexposure) pulmonary function testing was performed in the early afternoon, and 18-hr (postexposure) pulmonary function testing was done the next morning. Pulmonary function testing was conducted with the subject in the sitting position. We measured forced expiratory volume in 1 sec (FEV_1) using a rolling seal spirometer according to American Thoracic Society standards (*22*). Maximal flow–volume curves were measured by analyzing flow and volume signals with the rolling seal spirometer. We measured total lung capacity (TLC) by the single-breath helium dilution method (*23*), and we measured diffusing capacity (D_LCO) by the single-breath method of Ogilvie et al. (*24*).

Peripheral blood polymorphonuclear leukocyte concentration. Complete blood counts and differentials were obtained at baseline (preexposure) and at 18 hr postexposure to determine peripheral blood polymorphonuclear leukocyte concentrations. Blood counts and differentials were performed in the clinical laboratory of the University of California, San Francisco (USCF) Medical Center.

Bronchoscopy and bronchoalveolar lavage. Each subject underwent two BAL studies: a postexposure lavage conducted 20 hr after magnesium oxide fume exposure and a control lavage following exposure to medical-grade air. An interval of at least 28 days separated the postexposure and control lavages. Bronchoscopy included routine

Table 1. Age, sex, and smoking status of study subjects

Subject	Age (years)	Sex	Smoking status	Years since quitting smoking
1	43	Male	Never	NA
2	21	Female	Never	NA
3	31	Male	Never	NA
4	39	Male	Former	9
5	40	Male	Former	4
6	33	Female	Former	9

NA, not applicable.
Mean age ± standard deviation = 34.5 ± 8.0.

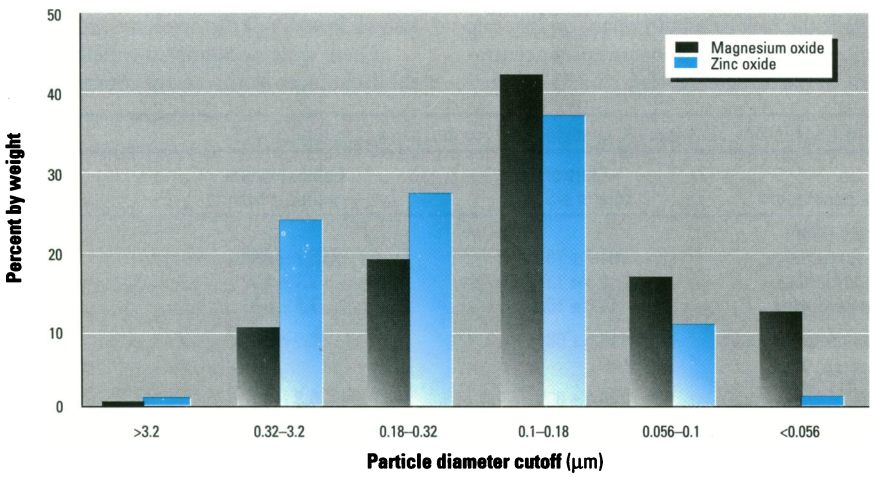

Figure 1. Diameters of furnace-generated magnesium oxide particles compared with those of zinc oxide particles. Particle size distribution was determined by micro-orifice uniform deposit impactor analysis. The total magnesium concentration during sampling was 90.6 mg/m^3. The total zinc concentration was 6.3 mg/m^3. See also Kuschner et al. (*20*).

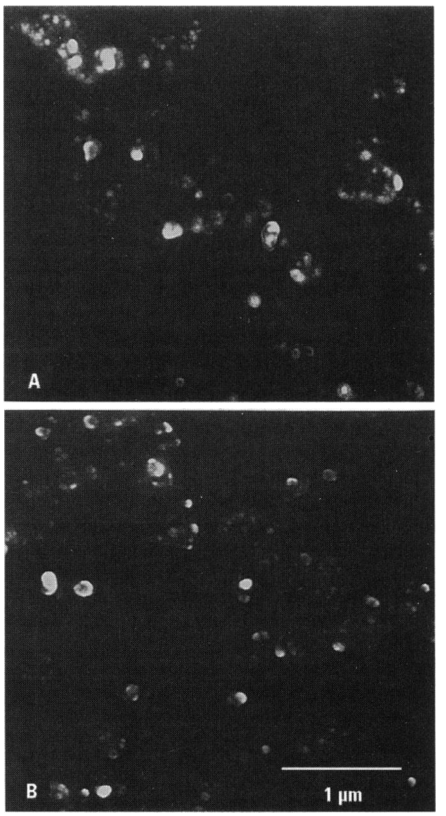

Figure 2. Magnesium oxide particles (A) and zinc oxide particles (B) on polycarbonate membrane with 0.015 µm pores. Bar at bottom right of photomicrograph represents 1 µm.

Table 2. Magnesium oxide fume exposure characteristics

Subject	Magnesium fume concentration (mg/m^3)	Exposure time (min)	Cumulative magnesium dose (min × mg/m^3)
1	5.8	45	261
2	230	15	3,450
3	210	20	4,200
4	123	45	5,535
5	110	45	4,950
6	143	45	6,435
Mean ± SD	137.0 ± 80.2	35.8 ± 14.3	4,138.5 ± 2,163.1

SD, standard deviation. The median fume concentration was 133 mg/m^3.

atropine premedication and topical anesthesia. A flexible fiberoptic bronchoscope (Pentax FB-19D; Pentax Precision Instrument Corporation, Orangeburg, NY) was wedged in a segmental airway in the right middle lobe, and BAL was performed by instilling four 50-ml boluses of 37°C isotonic saline and applying gentle suction until no further collection was noted. The BAL was collected on ice. The mean percentage ± standard error (SE) of instilled BAL fluid recovered was 70.0 ± 3.1% in the postexposure bronchoscopies and 70.1 ± 2.4% in control BAL studies ($p = 0.8$). BAL fluid was pooled but was not gauze filtered. We performed cell counts using a standard hemocytometer and differential counts after 5-min cytocentrifugation at 1,000 rpm and May-Grunwald-Giemsa staining.

Cytokine and protein determinations. BAL fluid supernatant was stored at -70°C for subsequent cytokine analysis. We quantified concentrations of tumor necrosis factor-α (TNF), interleukin (IL)-1 β, IL-6, and IL-8 in BAL supernatant by immunodetection with ELISA (R&D Systems, Minneapolis, MN). Each assay uses a quantitative immunometric sandwich enzyme technique, which we have described elsewhere (*20*). The lower limits of detection of the kits (supplier's data) were as follows: TNF, 0.085 pg/ml; IL-1, 0.083 pg/ml; IL-6, 0.080 pg/ml; and IL-8, 3.0 pg/ml. Nondetectable observations were assigned a value one-half that of the lower detection limit in later statistical analyses. The cytokines analyzed were above the lower limit of detection in all BAL specimens except for TNF in three cases (one subject both postcontrol and postexposure and one additional subject postexposure only) and IL-8 in two subjects (both postexposure). We determined BAL supernatant total protein concentrations using a commercially available colorimetric assay (Bio-Rad Laboratories, Hercules, CA).

Statistical analyses. We used the SAS standard statistical package for data analysis (SAS Institute Inc., Cary, NC). We compared by matched paired *t*-test: baseline with postexposure spirometry; baseline with postexposure peripheral leukocyte counts; and control with postexposure BAL cell and supernatant cytokine concentrations.

Table 3. Pulmonary function: 18 hr postexposure baseline difference

Pulmonary function measure	Mean ± SD postexposure baseline difference*
FEV_1 (liters)	0.0 ± 0.1
TLC (liters)	0.1 ± 0.2
D_LCO (ml/min/mm Hg)	0.9 ± 1.5

Abbreviations: FEV_1, forced expiratory volume in 1 sec; TLC, total lung capacity; D_LCO, diffusing capacity for CO; SD, standard deviation.
Baseline spirometry was performed in the afternoon; 18-hr spirometry was performed the following morning.
*p>0.20 for all differences.

Results

Symptoms, pulmonary function, and peripheral blood polymorphonuclear leukocyte concentrations. None of the subjects documented a fever or reported symptoms postexposure consistent with classic metal fume fever (myalgia, malaise, headache, or respiratory complaints). As shown in Table 3, there was no overall postexposure fall in pulmonary function; slight increases in TLC (mean increase of 100 cc) and D_LCO (mean increase of 0.9 ml/min/mm Hg) were not statistically significant. There was a mean decrease of peripheral blood polymorphonuclear leukocyte concentrations postexposure of $1.1 \times 10^{-3} \pm 1.0 \times 10^{-3}$ (SE)/mm^3 compared with baseline, which was also not statistically significant (p>0.3).

Bronchoalveolar lavage cells and cytokines. Mean BAL constituent concentrations postexposure and control are shown in Table 4. Overall, there were no statistically significant differences in concentrations of BAL neutrophils, macrophages, lymphocytes, or protein between postexposure studies and paired control values, nor any statistically significant postexposure increases in concentrations of any of the proinflammatory cytokines we studied (IL-1, IL-6, IL-8, and TNF).

Discussion

Inhalation of fine and ultrafine particulate magnesium oxide did not result in a symptomatic response or in any meaningful changes in lung function or in BAL concentrations of proinflammatory cells or cytokines at 20-hr follow-up. What might explain the lack of a pulmonary or systemic response following exposure to concentrations of particulates as high as 230 mg/m^3? Although it is certainly possible that the particle exposure concentrations used in this investigation were simply too low to result in a detectable clinical response, this would be inconsistent with ambient air pollution data. Untoward health effects have been associated with short-term particulate exposure in concentrations several orders of magnitude below those to which subjects in this study were exposed, in the microgram per cubic meter range. (*1–9,25*).

Particle size and dimension can be important determinants of toxicity, both because of delivered dose and through other morphologic mechanisms. It is possible that particles generated by our furnace system were different in size or shape from particles which, in other settings, have been linked with adverse health effects. In general, however, fine particles (diameters <2.5 µm) are thought to present the greatest health concern because they most easily enter the alveolar air space and because they may deliver more hits, or particles, per mass delivered. In our model, the vast majority of the furnace-generated particles were within respirable range and 98% were less than 1.8 µm. This would suggest that particle size and number per milligram, by themselves, do not provide a simple explanation for the lack of a response effect in our study. We cannot easily exclude potential effects of morphologic characteristics related to particle surface interactions.

It is possible that the follow-up time was either too early or too late to detect inflammatory changes in BAL. Our prior experience with zinc oxide, exposure to which is clearly proinflammatory, however, showed that 20 hr is an excellent time point to detect proinflammatory cytokine and cellular responses in the pulmonary microenvironment (*18–20*). Moreover, this follow-up time point is appropriate in view of the known kinetics of the cytokines studied.

There were no significant methodological differences in this study compared with

Table 4. Mean BAL constituents: postexposure–control paired analysis (n = 6)

BAL constituent	Control (mean ± SD)	Postexposure (mean ± SD)	p-Value
Cells (10^3/ml)			
Macrophages	194.7 ± 79.7	150.3 ± 69.5	0.12
Neutrophils[a]	2.3 ± 1.6	2.1 ± 1.2	>0.5
Lymphocytes	14.8 ± 10.9	7.9 ± 6.0	0.11
Total protein µg/ml	118.5 ± 68	56.5 ± 22.6	>0.7
Cytokines (pg/ml)			
TNF	0.3 ± 0.3	0.3 ± 0.2	>0.7
IL-1	0.1 ± 0.7	0.2 ± 0.7	>0.5
IL-6	2.1 ± 1.0	1.7 ± 0.8	>0.4
IL-8	14.3 ± 10.7	6.7 ± 4.2	0.20

Abbreviations: BAL, bronchoalveolar lavage; SD, standard deviation; TNF, tumor necrosis factor α; IL, interleukin. Postexposure BAL was performed 18–20 hr after magnesium oxide fume exposure.
[a]Neutrophils as a percent of total BAL cells = 1.5 ± 1.0% postexposure versus 1.1 ± 0.9% control (p = 0.27).

our previously reported study of pulmonary responses 20 hr after zinc exposure (*20*) except, of course, for the chemical composition of the particles studied (zinc oxide vs. magnesium oxide). In marked contrast with the benign response to magnesium oxide that we observed in this investigation, we previously found that purified ultrafine zinc oxide particle exposure results in dose-dependent increases in BAL neutrophils, IL-8, and TNF (*20*). We used protocols that were essentially identical in the two investigations. We utilized the same specially adapted furnace system capable of producing freshly generated purified fume in both investigations. Furnace-generated metal oxide particles were well within respirable range and were predominantly under 1 µm in diameter in both studies. Insufficient cumulative dose would not appear to explain the benign response to magnesium compared with zinc. Indeed, mean cumulative magnesium dose (± SD) in this investigation, 4,138 ± 2,163 min × mg/m^3, was markedly greater than the mean cumulative zinc dose in our previous study, 537 ± 232 min × mg/m^3. The outcome measures we studied in the previous investigations, especially BAL cells and proinflammatory cytokines, were sufficiently sensitive to detect an inflammatory response, even with the small subject numbers and brief exposures employed.

Our findings would suggest that high-dose exposure to magnesium oxide fume may not necessarily be acutely toxic. Further, our findings argue against the hypothesis that adverse health effects are attributable to a generic particle exposure effect. That is, the chemical composition of a particle, in addition to its physical properties and exposure dose, appears to have a relevant influence on inhalant toxicology. Health effects are not strictly a function of particle size and number.

We would not argue that magnesium oxide inhalation is benign under all circumstances. Approximately 70 years ago, Drinker and Drinker observed adverse effects in both animal and human exposures to magnesium oxide fume (*26,27*). These effects included a metal fume feverlike response in humans (maximum 580 mg/m^3) (*27*). Indeed, these are the only other controlled human exposures to magnesium oxide reported in the medical literature. In 1983, Hartmann et al. (*28*) reported that seven workers in a foundry developed fever following the introduction of a new founding technique that led to magnesium oxide fume exposure. Modification of the production system, with reduction of magnesium oxide fume generation, was associated with cessation of febrile episodes among workers. However, no industrial hygiene data were provided to quantify exposure levels. In 1992, Takac (*29*) reported morphologic changes in the microstructure of organs, including lungs, of animals exposed to magnesite waste containing largely magnesium oxide. Rats and rabbits were used to biologically monitor the accumulation and effects of inhaling air contaminated by the magnesite industry in two locations in Czechoslovakia. Study animals were exposed to contaminated air for 6 months. Findings included alterations in ciliary length, the presence of Curshman's spirals in smears of pulmonary lavages, and minor goblet cell abnormalities. Again, however, no industrial hygiene data were provided to quantify exposure levels.

In summary, we found no evidence of any pulmonary inflammatory responses following short-term fine and ultrafine particle inhalation to high concentrations of magnesium oxide. Based on our previous experience with zinc oxide, we cannot explain this lack of response by insufficient exposure, insensitive measures of response, or small study size. This investigation suggests that the toxicology of metal oxide particles is not determined simply by particle size characteristics alone (i.e., the number of particles per milligram inhaled). Hypotheses of air pollution effects associated with inhalation of fine particles (<2.5 µm diameter) should heavily weigh chemical-specific mechanisms that may modify the dose response depending on the particle inhaled.

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