WTC $PM_{2.5}$ were derived from settled dust collected at several locations around Ground Zero on September 12 and 13. Chemical analysis showed high levels of calcium sulfate and calcium carbonate. Aspirated samples of WTC $PM_{2.5}$ induced mild to moderate degrees of pulmonary inflammation one day after exposure, but only at a relatively high dose (100 micrograms). This response was not as great as that caused by 100 μg $PM_{2.5}$ derived from residual oil fly ash (ROFA) or Washington DC ambient air PM (NIST 1649a). However, this same dose of WTC $PM_{2.5}$ caused airway hyperresponsiveness to methacholine aerosol comparable to NIST 1649a and to a greater degree than ROFA. Mice exposed to lower doses by aspiration or inhalation exposure did not develop significant inflammation or hyperresponsiveness. These results show that a high dose of WTC $PM_{2.5}$ can promote mechanisms of airflow obstruction in mice. Airborne concentrations of WTC $PM_{2.5}$ which would cause comparable doses in people are high but conceivable in the immediate aftermath of the collapse of the towers. We conclude that a high-level exposure to WTC $PM_{2.5}$ could cause pulmonary inflammation and airway hyperresponsiveness in people. The effects of chronic exposures to lower levels of WTC $PM_{2.5}$, the persistence of any respiratory effects, and the effects of coarser WTC PM are unknown and were not components of these studies. Degree of exposure and respiratory protection, individual differences in sensitivity to WTC $PM_{2.5}$, and species differences in responses are important elements in the health risk assessment of WTC $PM_{2.5}$. [This abstract does not necessarily reflect USEPA policy.]

288 APPROACHES TO EVALUATION OF POTENTIAL HUMAN EXPOSURES AND HEALTH IMPACTS ASSOCIATED WITH AIRBORNE CONTAMINANTS FROM WORLD TRADE CENTER COLLAPSE/FIRES.

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The 9/11/01 World Trade Center (WTC) attack resulted in dispersal of numerous potentially toxic materials in the dust/smoke cloud that enveloped lower Manhattan and extended over other New York City (NYC) areas. The US Environmental Protection Agency (U.S. EPA) worked quickly with numerous other Federal, State, and local government agencies to mobilize emergency response efforts. This included cooperative actions to expand rapidly monitoring capabilities by which to measure environmental contamination derived from the 9/11 attack, the collapse of WTC buildings, the ensuing WTC Ground Zero fires, and WTC rescue/recovery operations. Environmental sampling was also carried out by others, e.g., academic investigators sponsored by various government agencies. This paper will mainly illustrate approaches employed, under challenging circumstances and time constraints, to evaluate potential human exposures to WTC-derived airborne pollutants and possible associated human health impacts, based on integrating information derived from: (a) analyses of composition of dust deposited from collapse of WTC buildings and associated toxicity testing of such dust; (b) data from ambient air monitoring at WTC Ground Zero, its immediate perimeter, and at sites in lower Manhattan and elsewhere in NYC metropolitan area; (c) preliminary results of meteorologically-based modeling of WTC plume movement/dispersal; (d) comparison of monitored or estimated concentrations against historical pollutant levels in NYC or other US urban areas; and (e), for those substances discernibly elevated above typical background levels, comparison against health benchmark values judged to be indicative of low risk for adverse health effects due to acute and/or prolonged exposures. [This abstract does not necessarily reflect USEPA policy.]

289 INDOOR AIR ASSESSMENT FOR THE WORLD TRADE CENTER SITE: SELECTING CONTAMINANTS OF POTENTIAL CONCERN AND SETTING HEALTH-BASED BENCHMARKS.

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As the clean-up and ambient air monitoring of the World Trade Center site comes to an end, health and environmental agencies are directing resources to evaluate the indoor environment for the presence of pollutants that might pose long-term health risks to local residents. Based on historical knowledge of building collapses/fires and review of both outdoor and limited indoor sampling data, six contaminants of potential concern (COPCs) were identified: lead, dioxin, PAHs, asbestos, fibrous glass and crystalline silica. Health-based benchmarks for indoor air and settled dust for each of these COPCs were developed to serve as clearance criteria. Existing environmental standards were utilized where appropriate. The Housing and Urban Development (HUD) standard for lead in settled dust (40 $\mu g/ft^2$) and the National Ambient Air Quality Standard (1.5 $\mu g/m^3$) were employed in this manner. In the absence of existing standards, risk-based clearance levels were developed employing IRIS verified toxicity factors and a residential exposure scenario (30 year duration). Health-based benchmarks for asbestos, dioxin and PAHs were developed in this way. Finally, for substances lacking a widely recognized environmental toxicity assessment, occupational standards with added safety factors were employed. Clearance criteria for fibrous glass and crystalline silica were derived by adding a safety factor of 100X to existing occupational standards.

290 DERMAL EXPOSURE LEADING TO RESPIRATORY TRACT SENSITIZATION AND DISEASE: A TRIVIAL OR CRITICAL LINK?

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Exposure to allergens resulting in respiratory tract sensitization has classically been considered to occur by inhalation. Increasing evidence from epidemiological and clinical studies and data from animal models support the hypothesis that dermal exposure may lead to respiratory sensitization and resultant alterations in pulmonary function. Permeation studies have demonstrated the potential for proteins as well as low molecular weight chemicals to penetrate the skin and mechanistic studies have demonstrated the skin to be a permissive site for the induction of Th2 responses. Animal models have been used to demonstrate specific and non-specific increases in airway hyper-reactivity following dermal exposure to allergens. Using latex allergy, chronic beryllium disease and allergy to low molecular weight chemicals as examples, these presentations will lay the ground-work for a discussion of the relevant clinical and experimental data and the mechanistic basis for the role of skin contact in the development of respiratory sensitization. Only by understanding the mechanisms of sensitization can effective intervention strategies be implemented to protect against respiratory allergens.

291 INFLUENCE OF DERMAL EXPOSURE ON THE DEVELOPMENT OF SENSITIZATION OF THE RESPIRATORY TRACT TO CHEMICAL ALLERGENS.

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Many chemicals are able to cause skin sensitization and allergic contact dermatitis. Fewer in number have been shown to cause allergic sensitization of the respiratory tract; among these being certain diisocyanates, acid anhydrides, reactive dyes and platinum salts. It is often assumed that sensitization of the respiratory tract to chemical allergens is induced exclusively following inhalation exposure. However, an argument can be made on the basis of theoretical considerations, experimental data and anecdotal clinical evidence that this is not necessarily the case. Allergy, by definition, requires the stimulation of a specific immune response and there is reason to suppose that the responses which result in allergic sensitization will normally be systemic in nature. In theory, therefore, dermal exposure to a chemical respiratory allergen may provoke the vigor and quality of immune responses necessary for effective sensitization of the respiratory tract. The results of experimental studies support this argument since it has been shown for instance that topical or intradermal exposure of guinea pigs to a known chemical respiratory allergen is able to sensitize animals such that subsequent inhalation challenge with an aerosol of the same chemical will provoke a respiratory hypersensitivity reaction. Taken together, the available evidence suggests that in certain circumstances respiratory sensitization to chemical allergens may be achieved by dermal exposure.

292 DERMAL EXPOSURE TO TRIMELLITIC ANHYDRIDE (TMA) POWDER INDUCES AIRWAY SENSITIZATION IN AN ANIMAL MODEL.

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TMA is a low-molecular-weight chemical used as a dry, fine powder by industry. Specific IgE and subsequent occupational asthma have been reported in exposed workers. The respiratory tract is considered to be a major route of TMA exposure, but dermal exposure is also possible. The role of exposure route in the development of TMA asthma is not known. The present study investigated the potential role of dermal exposure to dry TMA powder in both immunological sensitization and subsequent pulmonary responses to TMA inhalation challenge using the Brown Norway rat. Various doses of TMA were applied to the back (hair clipped carefully with scissors) on day 0, 7, 14 and 21, occluded with surgical tape and washed away after overnight, or after 5 hours of non-occluded exposure. Sera were collected on day 0, 7, 14, 21, 28 and 35 for specific IgE test. Exposed skin was also taken for morphologic study. TMA aerosol challenge was performed on day 35 and respiratory parameters including enhanced pause (Penh) recorded overnight.

Bronchoalveolar lavage was performed and pulmonary eosinophils assessed. The application area appeared normal, without any sign of inflammation examined grossly or microscopically. Immunohistochemical study (with one exposure only) found TMA-adduct staining in the stratum corneum and hair follicle. Specific IgE was noted by day 14 and levels were TMA dose-dependent. Eosinophilic inflammation and both early (EAR) and late airway response (LAR), were observed after airway challenge. EAR subsided within 30 min following challenge. LAR typically began 2 or more hours following challenge and persisted longer than 8 hours. TMA specific IgE and airway responses occurred in both occluded and non-occluded dermally exposed rats. Dermal exposure to dry TMA powder can induce specific-IgE and subsequent asthmatic-like EAR and LAR following TMA aerosol challenge. This model may be useful for mechanism study of dermal exposure and asthma from low-molecular-weight chemicals.

293 THE ROLE OF DERMAL EXPOSURE IN THE DEVELOPMENT OF LATEX ALLERGY.

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Latex allergy remains a serious risk for health care workers with past prevalence rates reported to range from 2.7-12%. Exposure may occur through inhalation as latex proteins bind to glove powders and are aerosolized during donning and removing gloves or through dermal exposure. Although hand dermatitis has been accepted as a risk factor, little is known of the relative contribution of the two routes of exposure to the development of sensitization. Animal models (BALB/c mice and hairless guinea pigs) have been used to evaluate the role of dermal exposure in the development of latex sensitization and to compare the potential for sensitization by the two routes. *In vitro* penetration studies using human surgical specimens and hairless guinea pig skin have demonstrated the importance of skin condition in the penetration of latex proteins with less than 1% of the applied dose of non-ammoniated latex (NAL) penetrating intact skin while as much as 30% penetrated through abraded skin. Exposure of BALB/c mice to 25µg NAL every 5th day by the dermal or intratracheal (i.t.) routes resulted in similar levels of latex specific IgE as measured by ELISA. A robust latex specific IgA response was seen in animals exposed by the i.t. route as compared to the dermal route. Upon respiratory challenge with methacholine, non-specific airway hyper-reactivity was dose-responsively increased and positively correlated with total IgE levels in animals exposed to latex proteins by either the i.t. or dermal routes. Immunoblot analysis revealed a different spectrum of sero-recognition of individual latex protein when exposure was *via* the i.t. versus the dermal route. Intervention strategies have been aimed at reducing the powder and latex protein content of gloves. Although these efforts have been observed to reduce the prevalence of symptoms in sensitized individuals, these data raise concerns regarding dermal exposure resulting from the continued use of low protein latex gloves. This work was supported in part by NIEHS interagency agreement #Y1-ES-0049-03.

294 INCLUSION OF SKIN EXPOSURE REDUCTION IN A TOTAL HYGIENE PROGRAM TO REDUCE EXPOSURE TO BERYLLIUM: BACKGROUND AND RESULTS.

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Recent epidemiological studies show no or very weak association between the mass concentration of beryllium in air, the traditional metric of exposure, and the prevalence of sensitization to beryllium or chronic beryllium disease. In general in the USA beryllium workplaces have permitted unlimited skin contact with beryllium solutions or particulate. In 1998 the possibility that sensitization to beryllium might occur *via* the skin was raised. Since then measures have been introduced to reduce skin exposure to beryllium solutions and particulate. Also taken were measures to reduce lung exposure to beryllium as well as dispersion of beryllium by various pathways within the workplace. Early data suggests these measures together reduce sensitization to beryllium.

295 GENOMIC MARKERS OF NEPHROTOXICITY IN FEMALE CYNOMOLGUS MONKEYS.

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The emergence of genomic technologies has led to a focused effort to identify early predictive markers of target organ toxicity. We define gene expression changes that correlate with the onset of histopathlogical lesions as genomic indicators of toxicity. For a genomic target to be considered an early predictive marker its expression pattern must quantitatively change before the development of the lesion, and the magnitude of change should intensify with the detection of histopathology. We have studied quantitative gene expression changes in the kidneys of female cynomolgus monkeys dosed with gentamicin (10 mg/kg) and/or everninomicin (30 or 60 mg/kg), an experimental oligosaccharide antibiotic, for seven days. Both drugs have been demonstrated to cause renal tubular necrosis and degeneration in rodents and non-human primates. Monkeys receiving both drugs showed renal lesions as early as day 1, consistent with a potentiation mechanism of gentamicin on everninomicin toxicity. By day 7 monkeys dosed with 60 mg/kg everninomicin alone also developed renal lesions, while the group exposed to both compounds had more extensive renal damage. The modulation of several genes previously identified to be associated with nephrotoxicity in rodent models was confirmed using quantitative real-time PCR. Among these, c-myc, c-jun, and MMP-9 exhibited changes consistent with the definition of a genomic marker of toxicity. Logistic regression modeling demonstrated a high degree of correlation between changes in gene expression and the development of histopathology. In addition, we identified a candidate early marker of toxicity. The expression of clusterin, a protein previously associated with renal necrosis, was significantly different from control levels (≥2-fold change) on day 1, and its level of expression was greater on day 7. These results provide the first data confirming gene expression changes associated with rodent nephrotoxicity in a non-human primate model, and are the first step in the validation of clusterin as an early marker for nephrotoxicity.

296 EXPRESSION OF GENES ASSOCIATED WITH DRUG-INDUCED BILIARY HYPERPLASIA AND CELL PROLIFERATION IN CYNOMOLGUS MONKEYS.

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Bile duct hyperplasia (BDH) can develop following administration of certain drugs. It is an important health concern because there are no predictive biomarkers for BDH that would allow adequate patient monitoring in the early stages. BDH arises as a consequence of cell proliferation within the hepatobiliary tree. We have investigated gene expression changes associated with BDH and cell proliferation in Cynomolgus monkeys treated with an experimental S-P compound. Histopathological evaluation of the livers and determination of a BrdU labeling index (BrdU-LI) for the biliary epithelium were used to separate the treated monkeys into good responders (BDH and high BrdU-LI), poor responders (BDH and low BrdU-LI) and non-responders (no BDH and no change in BrdU-LI). RNA isolated from the livers of these monkeys was hybridized on the Affymetrix U133 human genome chip. Analysis of this data with the GeneLogic Gene Express software revealed gene expression changes associated exclusively with monkeys in each of the good-, poor- and non-responder groups. There was limited overlap between the histopathological results for individual monkeys in each of these groups and between gene sets in these groups. Some of the genes that overlap include cyclins and other genes associated with cell proliferation. We identified 13 gene expression changes that discriminate between good- and non-responders, 63 for discrimination between good- and poor responders, and 23 for discrimination between poor- and non-responders. We also identified 5 gene expression changes that would discriminate between groups of monkeys with hyperplasia and those with no hyperplasia, 7 for high BrdU and low BrdU, and 2 for both of these effects. The predictive value of these changes will be evaluated further with quantitative PCR.

297 GENE EXPRESSION PROFILING OF NORMAL MAMMARY TISSUES FROM RAT STRAINS SENSITIVE AND RESISTANT TO MAMMARY CARCINOGENESIS.

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While human genetic linkage analyses have identified tumor suppressors that are responsible for familial breast cancer, many susceptibility genes are likely to be partially penetrant, due to the modifying effects of diverse genetic backgrounds and gene-environmental interactions. The advantage of using animal models to study inherited cancer susceptibility genes is the ability to use carefully controlled carcinogen exposure in highly inbred strains of animals. Consequently, breast cancer suppressor mutations that would have low penetrance in the human population may present as highly penetrant phenotypes in experimental tumor models. To gain insight into gene-environmental interactions in mammary carcinogenesis, we compared gene expression profiles in normal mammary glands from the sensitive Fisher 344 and resistant Copenhagen rat strains. Gene expression profiles were compared