553 13 WEEK INHALATION TOXICITY STUDIES OF 2-CYCLOHEXENE-1-ONE.

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2-Cyclohexene-1-one (CHX) is a cyclic α,β-unsaturated ketone with broad human exposure. CHX is an environmental pollutant and is present in tobacco smoke and soft drinks sweetened with cyclamate. Prechronic toxicity studies were conducted to provide data required to design chronic toxicity and carcinogenicity studies of CHX. Groups of 10 male and female F344 rats and B6C3F1 mice were exposed to 0, 2.5, 5, or 10 ppm CHX for 6 hr/day for 13 weeks. All animals survived until sacrifice. Microscopic lesions included hyperplasia, and squamous metaplasia in the nasal cavity in rats and mice of both sexes at all doses. Erosion and suppurative inflammation also occurred in high dose mice. Larynx and lung were not affected in either sex-species. Dose related centrilobular cytoplasmic vacuolation was seen in male rats only. Body weights were not significantly different from controls after 13 weeks of exposure. Liver/body weights were increased in male and female mice exposed to 5 and 10 ppm, and in male and female rats exposed to 10 ppm CHX. No adverse effects on sperm motility or vaginal cytology were observed. These data will be used in the design of a 2-year inhalation bioassay of CHX.

554 CYTOTOXICITY OF ABRASIVE BLASTING SUBSTITUTES.

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Increased morbidity and mortality from sandblasting with crystalline silica continues to occur even when respiratory protection is used. Because of the high risk of acute silicosis and increased mortality associated with the use of silica in sand blasting, it is banned in many industrialized countries and many substitutes are now being commercially used. We studied few of the most frequently used substitutes for *in vitro* cytotoxicity and tested aerosolized dusts within two hours of blasting and after aging for four weeks. Treated sand, sand, garnet, coal slag, specular hematite, and staurolite were collected by drawing air from a blasting area through a cyclone precipitator and then onto a 47 mm, 0.8 μm FWS-B filter within one meter of the operator's breathing zone. Samples of the pre-blasted and post-blasted materials were used for chemical and electron microprobe analyzes and compared. Samples prepared on polycarbonate filters were analyzed by scanning electron microscopy, x-ray spectrometry, and plasma emission spectrometry. Cytotoxicity studies using rat alveolar macrophage monitored cell viability, and leakage of lactate dehydrogenase (LDH) and N-acetyl-β-D glucosaminidase (NAG). Measurements of hydroxyl radical (•OH) generation and lipid peroxidation potential were also made on blasted dusts. The blasting process changed the trace metal content of all the blasted particles. Blasting generally increased the relative proportion of iron in blasted materials. This iron was apparently derived from the steel plates that were blasted. Blasting also resulted in the generation of particles with an average diameter of 1 μm. Both fresh and aged blasted particles decreased rat alveolar macrophage viability and increased enzyme release to varying degrees. Toxicity was generally more distinct for staurolite, coal slag, and garnet compared to sand. The •OH generation from all freshly blasted particles was generally higher than from aged particles. Lipid peroxidation potential was greatest for garnet and staurolite. This study demonstrates that silica sand blasting substitutes are not without biological effects and in some instances the cytotoxicity exceeds that of sand and may provoke lung injury.

555 GAMMA SCINTIGRAPHY OF RADIOLABELED VIRUS FOR IN VIVO DETERMINATION OF THE DOSE DELIVERED TO TARGET ORGANS IN GENE THERAPY: APPLICATION TO ADENOVIRUS-CFTR ADMINISTERED AS AEROSOL IN BABOONS.

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Scintigraphy enables visualization and quantification of pharmaceutical products in the body, both accelerating exploratory research and validating toxicology protocols. For cystic fibrosis therapy via inhalation of CFTR gene vectorized by adenovirus, optimization of aerosol is a prerequisite to obtain a functionnal CFTR in central lung. In preclinical efficacy and safety evaluations, imaging of virus is the only non invasive technique to quantify the lung deposition and baboon is the most relevant species for predictive studies on lung aerosol deposition in humans. Therefore adenovirus was administered to baboons as an aerosol, technetium 99m being used to label adenovirus in such conditions that bioactivity was preserved. Particle size (MMAD) and dispersion (σ g) of the aerosol generated with a breath-activated jet nebulizer were determined using a cascade impactor connected to a pump modelizing baboon respiratory conditions. DTPA-99mTc scintigraphy was used as a reference prior to validation with 99mTc-adenovirus. Three baboons were submitted to scintigraphy, receiving 100 puffes of 99mTc-DTPA. A week later, 99mTc-adenovirus (7.7 10^9 pfu, 814-925 MBq, 2 ml) was administered. Lung regional deposition was assessed from Regions Of Interest corresponding to central and peripheral regions. Granulometry corresponded to a 1.6μ m MMAD with a 1.8 geometric dispersion.Nebulized fraction was 15-17% of the initial dose and total lung deposition 2.7 to 7.5% of the nebulized fraction. Regional deposition to the central lung was 1.0 to 3.5%. These results confirm that this technique allows to determine the actual dose delivered to the target organ. Furthermore, similarities observed between DTPA and virus deposition validates the use of DTPA scintigraphy as a pretherapeutic test for each patient.

556 AMIODARONE-INDUCED PULMONARY TOXICITY (AIPT) IN F344 RATS.

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Amiodarone (AD) is a very effective antiarrhythmic drug, but its side effects limit its clinical application. AIPT involves both pulmonary inflammation and fibrosis in humans. The goal of this study was to develop an animal model of AIPT and examine the possible mechanisms leading to its development. F344 rats were intratracheally instilled with AD (6.25 mg/kg with a 3.125 mg/ml solution) in sterile water or the sterile water vehicle on the first day and then again 48 hours later. Animals were killed 5 days after the initial treatment and bronchoalveolar lavage (BAL) was performed. AD-treated rats had increased neutrophils and eosinophils recovered in the BAL fluid. BAL cells from AD-treated rats produced more integrated phorbol-myristate-acetate-stimulated luminol-dependent chemiluminescent (LDCL) counts over 20 minutes than BAL cells from control rats. Experiments using specific inhibitors implicate peroxynitrite in at least part of the LDCL response. When rats were examined 28 days after the initial AD or vehicle treatments, lung fibrosis was present both biochemically and histopathologically in only the AD-treated animals. Hydroxyproline, an amino acid found in collagen and used as a biochemical indicator of fibrosis, was elevated in AD-treated rats compared to controls. Examination of sections of lung tissue revealed minimal to mild, multifocal, interstitial fibrosis in the AD-treated animals. These findings indicate this model exhibits the pulmonary inflammation and fibrosis similar to that occurring in human patients and that elevated immune and oxidative processes may be involved in the development of AIPT in this model. (Supported by NIH 5 T32 GM07039.)

557 POTENTIAL HEALTH EFFECTS OF DBPs USING QUANTITATIVE STRUCTURE TOXICITY RELATIONSHIP.

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Disinfection by-products (DBPs) are produced as a result of disinfecting water using various treatment methods. Over the years, chlorine has remained the most popular disinfecting agent due to it's ability to kill pathogens. However, in 1974, it was discovered that the superchlorination of drinking water resulted in the production of chloroform and other trihalomethanes. Since then hundreds of additional DBPs have been identified, including haloacetic acids and haloacetonitriles. Quantitative Structure Toxicity Relationship (QSTR) utilizes a computer based technology to assess the toxicity of a chemical solely from it's molecular structure. The current research was conducted utilizing the TOPKAT® / QSTR software package which is comprised of robust, cross-validated QSTR models, for assessing specific toxic endpoints. A total of 253 DBPs were analyzed using the carcinogenicity and developmental toxicity submodels of TOPKAT®.

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshop, roundtable, and poster sessions of the 38th Annual Meeting of the Society of Toxicology, held at the Ernest N. Morial Convention Center, New Orleans, Louisiana, March 14-18, 1999.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 419.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 444.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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