Society of Toxicology

40th Annual Meeting

An Official Journal of the
Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES

Formerly Fundamental and Applied Toxicology

The Toxicologist

DISTRIBUTION STATEMENT A
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20020522 109

Oxford University Press

Volume 60, Number 1, March 2001

after chronic exposure to TCE in drinking water (0, 1,000, or 10,000 ppb) in either female New Zealand Black/New Zealand White (NZB/NZW) or female B6C3F1 mice. These two strains of mice were used in this study because NZB/NZW mice spontaneously develop autoimmune disease while B6C3F1 mice do not. Over a 26-week exposure period, serum was collected at various intervals to monitor the development of antinuclear antibodies (dsDNA and ssDNA) and autoantibodies to the glomerulus basement membrane (GBM). In NZB/NZW mice, exposure to 1000 ppb TCE resulted in significantly increased autoantibodies to dsDNA and GBM at 16, 19, and 23 weeks. However, dsDNA autoantibodies were not evident in B6C3F1 mice until 26 weeks of exposure to 10,000 ppb of TCE. In addition, mitogenic lymphocyte proliferative responses were evaluated after 26 weeks of TCE exposure. No significant differences in any treatment group were observed in both strains of mice. Humoral immunity was assessed using the plaque forming cell (PFC) assay. The PFC response was dose-responsively decreased by 45% and 84% in the 1,000 and 10,000 ppb treatment groups in NZB/NZW mice, respectively. Further TCE studies are in progress to evaluate differences between NZB/NZW and B6C3F1 mice that will include comparative evaluation of PFC responses in B6C3F1 mice. Comparisons between the classic autoimmune and the standard immunotoxicological mouse models will facilitate improved risk assessment of TCE and its role in the development of autoimmune disease.

677 EFFECTS OF CONCURRENT EXPOSURE TO N,N-DIETHYL-*m*-TOLUAMIDE (DEET), PYRIDOSTIGMINE BROMIDE (PYR), AND EXERCISE STRESS ON BIOMARKERS OF IMMUNE FUNCTION IN B6C3F1 MICE.

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Soldiers returning from the Gulf War reported various manifestations including joint pain, muscle fatigue, headaches, myalgia, skin rash, and respiratory difficulties. It has been suggested that exposure to a mixture of xenobiotics may have contributed to these reported symptoms. Additionally, the effect of stress in combination with concurrent environmental exposures may have increased the toxicity of the xenobiotic mixture. PYR and DEET have been identified as two of the xenobiotics which may be causative agents. The combination of these chemicals with or without stress has been previously reported to increase neurotoxicity. Due to the complexity of the neuro-endocrine-immune axis it seems rational that the immune system may also be affected by these exposures either directly or indirectly through an effect on the nervous or endocrine systems. Previous range finding studies in this lab have determined a LOEL for these three exposures. In this study mice were exposed daily to the LOEL or 2 times the LOEL for 14 days. For both the LOELs (15.5 mg/kg DEET, 2 mg/kg PYR, and 20 min exercise stress) and the 2xLOELs (31.5 mg/kg DEET, 5 mg/kg PYR, and 40 min. exercise stress) no effect was noted in thymic or splenic weights or cellularity, in total serum IgM or IgG levels, in peripheral WBC or differential counts, or in CD4/CD8 lymphocyte subpopulations. NK-cell activity was, however, significantly increased over control by stress and stress mixture (DEET+PYR+Stress) treatments. T-cell proliferation was significantly suppressed following treatment with PYR, stress or the stress mixture. Interactions in the tertiary mixtures were not additive for any of the endpoints.

678 ESTIMATING RISK POSED BY DRINKING WATER DISINFECTION BY-PRODUCTS.

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Disinfection by-products (DBPs) result from the chemical disinfection of drinking water leading to human exposures through multiple exposure routes. Some epidemiological and toxicological reports of chlorinated drinking water for mixtures of DBPs and individual DBPs indicate that these chemicals may pose cancer and developmental hazards. The results of an approach to estimate risks posed by DBPs in drinking water is described here. In our approach to quantify human health risks, we divided DBPs into three groups. Group A which accounts for up to 50% of the total organic halides present in treated drinking water, can be quantified using routine gas chromatography (GC) and GC/ Mass Spectroscopy (MS). Several hundred other halogenated DBPs, which cannot be quantified by routine GC and GC/MS comprises Group B. Group C is comprised of non-halogenated DBPs. The risks posed by chemicals potentially comprising Group B was evaluated using a Quantitative Structure Toxicity Relationship (QSTR) model and measures of total organic halide. The fractions of Group B DBPs found to be associated with cancer and developmental toxicity by using QSTR are 58% and 42%, respectively. Mixtures risk posed by chemicals comprising Group A was assessed using animal bioassay data and response addition. The risk estimates for the Group B DBPs for each health effect were quantified by combining exposure estimates with dose-response functions for the Group A DBPs. The DBP risks were increased over the risk predicted for Group A alone by 58% and 42% for cancer and developmental toxicity. EPA convened an expert panel to further evaluate the potential risks posed by Groups B and C. Some of the conclusions of the workshop include, 1) substantial fractions of DBPs associated with major disinfectants are not well characterized; 2) risks should be evaluated using other approaches such as, whole mixture assessment, and incorporation of mode/mechanism of action data.

679 AMES MUTAGENIC AND DEVELOPMENTAL TOXICITY POTENTIAL OF HAAS USING QUANTITATIVE STRUCTURE TOXICITY RELATIONSHIP.

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QSTR models can be used to predict toxic effects such as mutagenicity and developmental toxicity. Such models can be a useful component of hazard identification in Chemical Risk Assessment; especially in cases were there is a paucity of toxicology data. Haloacetic acids (HAAs) along with trihalomethanes (THMs), haloacetonitriles (HANs) and other disinfection by-products (DBPs) are produced as a result of disinfecting water. THMs are the most commonly occurring group of DBPs in drinking water followed by the HAAs. Both the THMs and HAAs are comprised of a series of halogenated analogues; however, the brominated and iodinated analogues are less well characterized toxicologically. In the absence of toxicological data regarding the mutagenicity and developmental toxicity of the entire class (12 HAAs), QSTR submodels were used to assess these health-related endpoints. With respects to the toxicology of HAAs, the chlorinated analogs in contrast to the brominated and iodinated analogues have been more throughly characterized. Dichloroacetic acid (DCA), and trichloroacetic acid (TCA) occur at significantly higher concentrations than monochloroacetic acid (MCA) and have more toxicity data than monochloroacetic acid (MCA). The mono- and tri- halogenated analogues were predicted as developmental toxicants. However, only the mono- and a few of the di-halogenated acetic acids were predicted to be mutagenic. An analysis of the electrotopological values (E-state descriptors) for developmental toxicity demonstrated that the electronegativity of all the halogen descriptors within classes (*e.g.*, mono, di and tri HAAs) were constant and hence shows no demonstrated effect upon this particular health-related endpoint compared to mutagenicity where the magnitude of the E-State values varied within and between classes of these analogues according to the electronegativity of the halogens.

680 CHEMICAL-SPECIFIC, CANCER RELEVANT CELLULAR ALTERATIONS AS BIOMARKERS FOR DISINFECTANT BYPRODUCT EXPOSURE.

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Chemical disinfection of public drinking water supplies results in the formation of disinfection byproducts (DBPs). Some of these DBPs have produced cancer in research animals, which has stimulated epidemiologic studies in humans. The carcinogenic mechanism of some DBPs is thought to be genotoxic involving interaction with cellular DNA, while others exert non-genotoxic tumor promotional effect. Hazard assessment of the DBPs requires determination of their carcinogenic risk, if any in drinking water. The DBPs of interest were chloropicrin, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), dichloroacetic acid, the haloacetonitriles, bromate, and bromodichloromethane. These DBPs were reviewed with the aim of identifying molecular and biological markers for use in molecular epidemiology to establish an association between their exposure and cancer in humans. The DBPs, except for dichloroacetic acid, produced mutagenic and genotoxic alterations in microbial, cell culture and in vivo test systems. Some DBPs also appeared to promote the expansion of precancerous cells containing some of the molecular events of cancer. In general, potential molecular marker in tumors were deemed not to be specific for the DBPs and, thus, would not be usefully employed as chemical specific biomarkers in studies of human tissues. There were a few exceptions, including the possible genotoxic activity of bromodichloromethane and the use of possible hemoglobin adducts of bromodichloromethane and haloacetonitriles. Although hemoglobin adducts would not demonstrate a linkage between exposure and cancer in humans, it could indicate exposure.