blockers. To determine the accuracy with which HERG-Lite predicts hERG risk, we are screening an 1120 compound library from Prestwick Chemical Company in HERG-Lite and FASTPatch (FP), our automated patch-clamp system. To date, 611 compounds have been tested in both assays: HL at 1, 10 and 30 μM and FP at 10 μM. There is 90% agreement between the hERG assays with respect to hERG risk prediction. Of the 611 compounds screened, 338 (~55%) are null in both assays while 273 (~45%) were positive in one or both of the assays. Of those 273, 131 were predicted to be blockers in HL and have been confirmed in FP, 62 were identified in HL and FP as dual risk compounds, i.e. both direct block and trafficking inhibition, and 17 were shown to be trafficking inhibitors without block. Importantly, 29% of hERG blockers are also trafficking inhibitors. Overall the incidence of hERG trafficking inhibition in the Prestwick library is 12.9% making this an important consideration in hERG risk assessment. In this first round of screening, the incidence of HL false negatives for blockers was only 3.3% as 20 compounds showed greater than 15% hERG current inhibition in FP but no significant rescue of hERG-SM. Forty-three compounds (~7% of the total) rescued hERG-SM but were not detected as blockers in FP. These may be FP false negatives or they may be rescuing hERG-SM without block. If the latter possibility is correct, these compounds may be useful hERG "agonists" by increasing channel surface expression.

1358 BRADYARRHYTMIA INDUCED BY OXIDANT ATMOSPHERE INHALATION IN CONSCIOUS RATS. A TELEMETRY STUDY IN HEALTHY AND MYOCARDIAL INFARCTED (MI) RATS.

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Increasing evidences of cardiorespiratory responses to urban atmospheric pollutant have been published during the past few years. The oxidant potential of Diesel emissions has increased due to oxidation catalysis setup. This can be probed by the NO2/NOx ratio which correlates with the amount of reactive oxygen species to be generated during the test atmosphere contact with aqueous media containing CPH as a spin probe and assayed by electron spin resonance (ESR). We assess the impact of inhalation for 3 hours of diluted untreated (UDE) (low oxidant) and Oxycat treated (ODE) (high oxidant) Euro3 Diesel engine emissions and of Ozone on Heart rate variability (RMSSD) and arrhythmia occurrence. Beat to beat interval (RR) time series were obtained using the ECG-Auto (EMKA Paris France) software from continuous telemetry recordings (DSI international). Automated analysis procedure of arrhythmia identification and quantification have been developed using a dynamic symbol encoding process application on RR time series. UDE proved to decrease RMSSD in both healthy and MI rats, and to induce extrasystoles and tachyarrhytmia in MI rats only. ODE, and ozone induced a marked bradycardia (increased RR values), and bradyarrhytmia, with a latent period of 1-2 hours. These bradycardia and bradyarrhytmia events which were never observed in unexposed healthy nor MI rats led to increased RMSSD and Shannon entropy values signing most probable impacts on heart autonomic control. While no adaptative process was evidenced upon repeated exposure to UDE, with ODE and Ozone, maximal impacts where seen at first exposure and reduced impacts where seen after 3 daily exposures when increased lung and heart SOD and GPx activity levels were observed signing activation of antioxidant defenses.
In conclusion, inhalation of atmospheres containing oxidant pollutants induce numerous arrhythmias in both healthy and MI rats. These arrhythmia may be part of the mechanisms contributing to the growing evidences of atmospheric pollutant induced cardiac injuries.

1359 A NOVEL MURINE MODEL OF OCCUPATIONAL RHINITIS FOLLOWING INHALATION OF TOLUENE DIISOCYANATE.

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Diisocyanates are low molecular weight chemicals that have been identified as the leading cause of occupational asthma. Epidemiological evidence suggests that diisocyanate-induced rhinitis is a comorbid and often preceding condition in patients with occupational asthma. Understanding the pathogenesis of occupational rhinitis and its biological and chronological relationship with asthma will be critical for disease prevention. In this regard, we have developed a murine model of toluene diisocyanate (TDI)-induced rhinitis. Female C57BL/6 mice were exposed to TDI vapor via inhalation for 4 hours/day for 12 days with or without a 2 week rest period and TDI challenge. The nasal mucosa was examined after each experimental stage for alterations in cytokine expression and pathology. Mice exposed to TDI vapor for 2 weeks showed elevated expression of IL-4, IL-5, IL-13, IL-10 and IFNγ suggesting a mixed Th1/Th2 immune response. Expression of proinflammatory cytokines (TNFα and IL-1β) and adhesion molecules (VCAM-1 and ICAM-1) was also upregulated. These cytokine changes corresponded to a marked influx of inflammatory cells into the nasal mucosa, eosinophils being the predominant cell type. Removal from exposure for 2 weeks resulted in a reduction in cytokine expression and pathology to control levels. Subsequent challenge with TDI vapor resulted in robust upregulation of the same cytokine genes as well as eosinophilic inflammation. The present model shows that TDI inhalation induces allergic rhinitis displaying many of the cardinal features of human disease. Future work will use this model to define the immune mechanisms and also examine the temporal/dose relationship between TDI-induced rhinitis and asthma.
The findings and conclusions in this abstract have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

1360 LEAD SKEWS THE DEVELOPMENT AND FUNCTION OF BONE MARROW-DERIVED DENDRITIC CELLS TOWARD THE TYPE-2 IMMUNE PHENOTYPE.

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Although lead (Pb) has significant effects on the development and function of macrophages, B cells, and T cells and has been suggested to promote allergic asthma in mice and humans, Pb modulation of bone marrow (BM)-derived dendritic cells (BM-DC) and the resultant DC effects on Th1 and Th2 development had not been examined. Thus, we developed BM-DCs with murine granulocyte macrophage-colony stimulatory factor (mGM-CSF) ± PbCl2 to evaluate any phenotypic changes of BM-DC derived in the presence of Pb (Pb-DC). Pb-DCs after ten days of development in vitro had significantly lower expression of CD11c. Although fewer CD11c+ DCs (% and MFI) were generated with Pb, Pb-DCs had significantly greater MHC class II (I-A) expression than the day-10 non-Pb-exposed DCs (DCs). However, these differences diminished upon LPS stimulation for two days. After LPS stimulation, CD80, CD86, CD40, CD54, and MHC-II were all up regulated on both Pb-DCs and DCs, but Pb-DCs expressed significantly less CD80 than DCs. The CD86:CD80 ratio suggests a PB-DC potential for Th2 cell development and enhanced immunity, since CD80 has preferential interaction with CTLA-4, which affects immunosuppression. After LPS stimulation, IL-6, IL-10, IL-12 and TNFα levels significantly increased with both Pb-DCs and DCs, although Pb-DCs produced significantly less cytokines than DCs, except for IL-10, which further supports preferential skewing toward type-2 immunity by Pb-DCs. In vitro studies confirm that Pb-DCs have the ability to polarize antigen-specific T cells to Th2 responses. Pb-DCs also enhanced allogeneic and autologous T cell proliferation in vitro, and in vivo studies suggest that Pb-DCs inhibited Th1 effects on humoral immunity. The Pb effect was mainly on DC and not T cells, and its modification of DC function appears to be the main cause of its promotion of type-2 related immunity, which may relate to its enhanced activation of the Erk/MAP kinase pathway.

1361 CONTACT AND RESPIRATORY CHEMICAL ALLERGENS INDUCE DIFFERENTIAL CUTANEOUS CYTOKINE SECRETION PATTERNS.

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Prolonged topical exposure of BALB/c strain mice to the contact allergen dinitrochlorobenzene (DNCB), or to the respiratory allergen trimellitic anhydride (TMA), promotes the selective development of type 1 and type 2 immune responses, respectively.The early events which may play a role in the initiation of polarized immune responses to different classes of chemical allergen are of particular interest.In the current experiments we have examined the kinetics of cutaneous cytokine expression induced following exposure of BALB/c mice to 1% DNCB or to 25% TMA. Expression of the proinflammatory cytokines tumor necrosis factor α (TNF-α) and interleukin (IL)-1β and the anti-inflammatory cytokine IL-10 has been analyzed by cytokine protein array. Groups of mice (n=10) were exposed on the dorsum of both ears to chemical 30 min, 2h, 4h, 24h, 48h and 72h prior to preparation of dorsal ear explants for culture on medium for 16h. Exposure to DNCB was associated with a rapid increase in TNF-α secretion 2h following exposure that had declined by 4h, and a subsequent up-regulation of IL-1β expression that was sustained from 4h to 72h. In contrast, treatment with TMA was associated with a very rapid induction of IL-10 (within 30 min) which did not return to basal levels until after 24h of exposure. At the later time points (24 to 72h), TMA stimulated increased expression of TNF-α and IL-1β. Taken together with previous observations on the tempo and vigor of epidermal Langerhans' cell (LC) migration by chemical allergens, this suggests that treatment with DNCB provokes the cytokine mileau (TNF-α and IL-1β) necessary for rapid and vigorous LC migration. In contrast, the early expression of IL-10 induced by exposure to TMA results in delayed kinetics of LC migration until later time points when the cytokine balance is in

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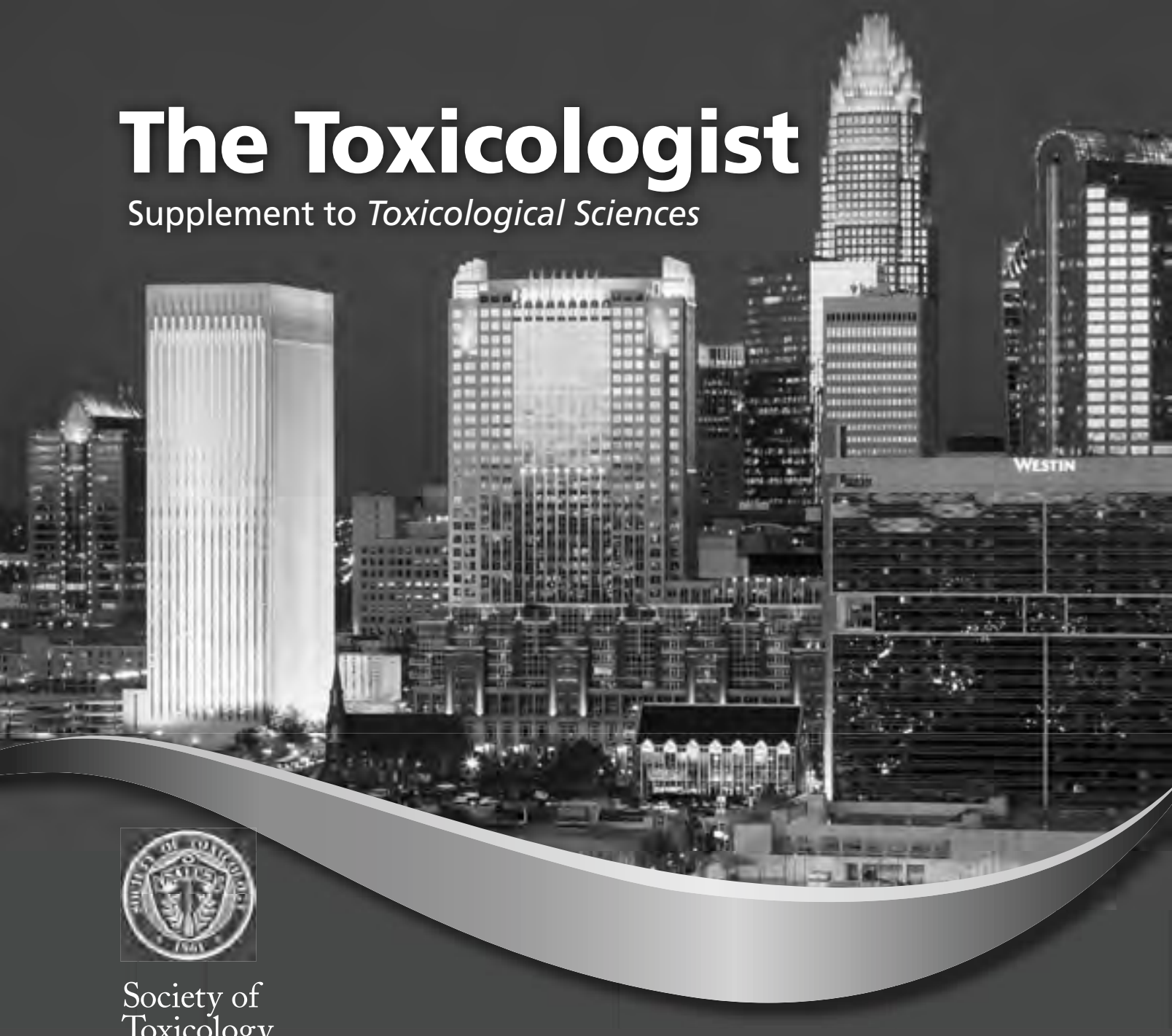

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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

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