pharmacokinetic uncertainties. Studies with the widely used herbicide 2,4-dichlorophenoxyacetic acid (2,4D) have demonstrated how internal dose measurements can be routinely and effectively quantified from animal dietary toxicity studies, a common mode of administration for many chemicals. In addition, units of internal dose common to human biomonitoring and toxicity studies can be further related to health protective regulatory reference standard doses, e.g., RfDs and RfCs, by development of "biomonitoring equivalent" (BE) values. Developed from pharmacokinetic modeling, BEs represent estimated blood/urine concentrations resulting from exposures to RfD/RfC exposure standards (Aylward et al., EHP 118: 177, 2010). These refinements to comparative internal dose quantitation offer important dose/exposure context to informing toxicologic plausibility and interpretation of observations reported in epidemiology studies.

W 50 THE ROLE OF EPIDEMIOLOGIC RESEARCH IN RISK ASSESSMENT: SOME CHALLENGES AND OPPORTUNITIES.

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Epidemiologic data obtained from well designed and executed human studies can inform the risk assessment process. Because of the nature of environmental and occupational exposures, most studies are observational in design and thus subject to numerous limitations; the primary limitation is typically the validity and reliability of exposure assessment. An overview of epidemiologic study design, with a focus on those studies most useful for risk assessment, will be presented. Traditional methods used for exposure assessment and absorbed dose measurement for registration and regulatory purposes will be reviewed, and contrasted with those typically used in epidemiologic research. Opportunities in exposure assessment in large occupational or environmental epidemiologic studies (such as the Ontario Health Study) and promising methods for incorporation of dose information into epidemiologic research will be discussed. Continued collaborative efforts amongst epidemiologists, exposure scientists, toxicologists, and risk assessors will be necessary to develop and apply the tools necessary to allow for the better integration of epidemiologic study results into the risk assessment process.

W 51 NEW TOOLS AND APPROACHES TO LINK TOXICOLOGICAL MODELS TO HUMAN HEALTH EFFECTS.

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Due to limitations on human testing, the use of surrogate models and endpoints are necessary when studying the effects of environmental chemicals on human health. However, translating the results obtained using the surrogate models and endpoints to human health effects poses many unique challenges. The development of new tools and approaches for linking toxicological models with human health effects will be highlighted using two examples. The first example focuses on the incorporation of human dosimetry and exposure into high-throughput in vitro toxicity screening. In this example, in vitro assays were used to estimate human metabolic clearance and plasma protein binding for ToxCast chemicals. Computational in vitro-to-in vivo extrapolation methods were then used to estimate the human oral equivalent doses that would be required to produce steady state in vivo concentrations equivalent to in vitro AC50 values from the high throughput screens. These oral equivalents were compared with human oral exposure estimates to assess whether significant in vitro bioactivity occurred within the range of expected human exposure. The second example focuses on the translation of biomarkers of effect from rodent models to humans. In this example, circulating mRNAs were evaluated as biomarkers of hepatotoxicity. In a rat model, increases in liver specific mRNAs were observed in the cell-free plasma of rats treated with two different hepatoxicants. Characterization of the circulating mRNAs showed an association with both necrotic debris and encapsulation within microvesicles. The increase in circulating liver mRNAs was confirmed in human subjects following drug-induced liver injury demonstrating translation of the biomarkers from animals models to humans.

W 52 THE ITERATIVE ROLE OF EXPOSURE SCIENCE IN RISK ASSESSMENT.

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The mapping of the human genome and the emergence of tools in computational, informational, and molecular sciences has led to new possibilities for improving chemical risk assessment. For the first time, these advances allow for a high throughput and broad scale examination of the molecular and cellular targets of chemicals. In 2007, EPA launched ToxCast™ in order to rapidly and cost-effectively prioritize the toxicity testing of a large number of chemicals. Because hazard and exposure mutually determine risk, the implementation of toxicity screening has led to awareness of the need to develop exposure screening approaches. Furthermore, there is the need to integrate the two approaches to focus toxicity testing on those chemicals and endpoints, at those life-stages and via those exposure routes, most likely to present a risk of concern (Dellarco et al., 2010). Thus, exposure assessment should not be relegated to the fourth step in risk assessment (following dose-response, as specified by the 1983 NRC "Red book") but rather should be considered iteratively with allocation of resources as guided by a risk screening approach. Herein, I describe approaches that make use of two types of exposure survey data, the National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey of population biomarkers, and national surveys of pesticide residues in homes and daycare facilities to inform development of risk assessment models for a group of pesticides. *EPA reviewed this work but it does not necessarily reflect official Agency policy.*

PL 53 ACUTE PULMONARY RESPONSES TO MWCNT INHALATION.

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The large scale manufacture of multi-walled carbon nanotubes (MWCNT) suggests occupational exposures may occur. In order to investigate the pulmonary toxicity of MWCNT, male C57BL6/J mice (6 weeks old) were exposed to aerosolized MWCNT (10 mg/m^3, 5 hours per day; mass mode aerodynamic diameter 1.3 μm, count mode aerodynamic diameter 0.4 μm) for 2, 4, 8 and 12 days. All mice were sacrificed at one day post-exposure. Whole lung lavage (WLL) was conducted and polymorphonuclear leukocytes (PMNs) were assessed to index pulmonary inflammation. WLL fluid assays included lactate dehydrogenase (LDH) activity as a measure of cytotoxicity, albumin as a marker of the lung air-blood barrier integrity, as well as various cytokines. MWCNT lung burden ranged from 6.6 ± 0.5 μg/lung (2 days exposure) to 30.6 ± 1.2 μg/lung (12 days exposure). MWCNT-exposure induced increases in PMN levels from 152 ± 27 (x 10^3) PMNs/mouse (2 days exposure) to 1,893 ± 462 (x 10^3) PMNs/mouse (12 days exposure). MWCNT-exposure increased WLL fluid albumin from 0.18 ± 0.01 mg/ml (2 days exposure) to 0.41 ± 0.04 mg/ml (12 days exposure), while WLL fluid LDH increased from 131 ± 6 units/L (2 days exposure) to 286 ± 35 units/L (12 days exposure). MWCNT exposure caused increased interleukin-6 (IL-6), chemokine ligands 1 and 2 (CXCL1, CCL2), and granulocyte macrophage colony stimulating factor (GM-CSF) levels relative to air-exposed controls. In summary, these data indicate that exposure to aerosolized MWCNTs results in dose-dependent increases in pulmonary inflammation and damage, suggesting that aerosolized MWCNT may pose an occupational health hazard.

PL 54 BIODEGRADATION OF CARBON NANOTUBES BY EOSINOPHIL PEROXIDASE.

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Single-walled carbon nanotubes (SWCNT) having high potential for applications in nanotechnology, electronics and medicine can have adverse effects on human health and the environment. In vitro data indicate that SWCNT may be cytotoxic, largely by inducing oxidative stress. It was shown previously, that horseradish peroxidase and human myeloperoxidase (MPO) catalyse the biodegradation of SWCNT. Biodegradation of nanotubes by another mammalian peroxidase - eosinophil peroxidase (EPO) has not been studied. EPO exocytosed by eosinophils is actively involved in increased oxidant production during lung inflammation after treatment with pollutants and cigarette smoke. We found that incubation with EPO and H2O2 caused degradation of CNT over time, and the CNT suspension turned translucent. Neither EPO alone nor H2O2 alone caused nanotube degradation. Degragation of CNT was confirmed by: 1) visible-near-infrared spectroscopy showing decrease of characteristic metallic band (M1) and semiconducting (S2) transition band and 2) Raman spectroscopy demonstrating increase of disorder-induced D-band and decrease of tangential-mode G-band. Drastic changes in nanotube morphology were demonstrated by transmission electron microscopy. Biodegradation of CNT was higher in the presence of NaBr suggesting that not only reactive radical intermediates of EPO but also generated HOBr was

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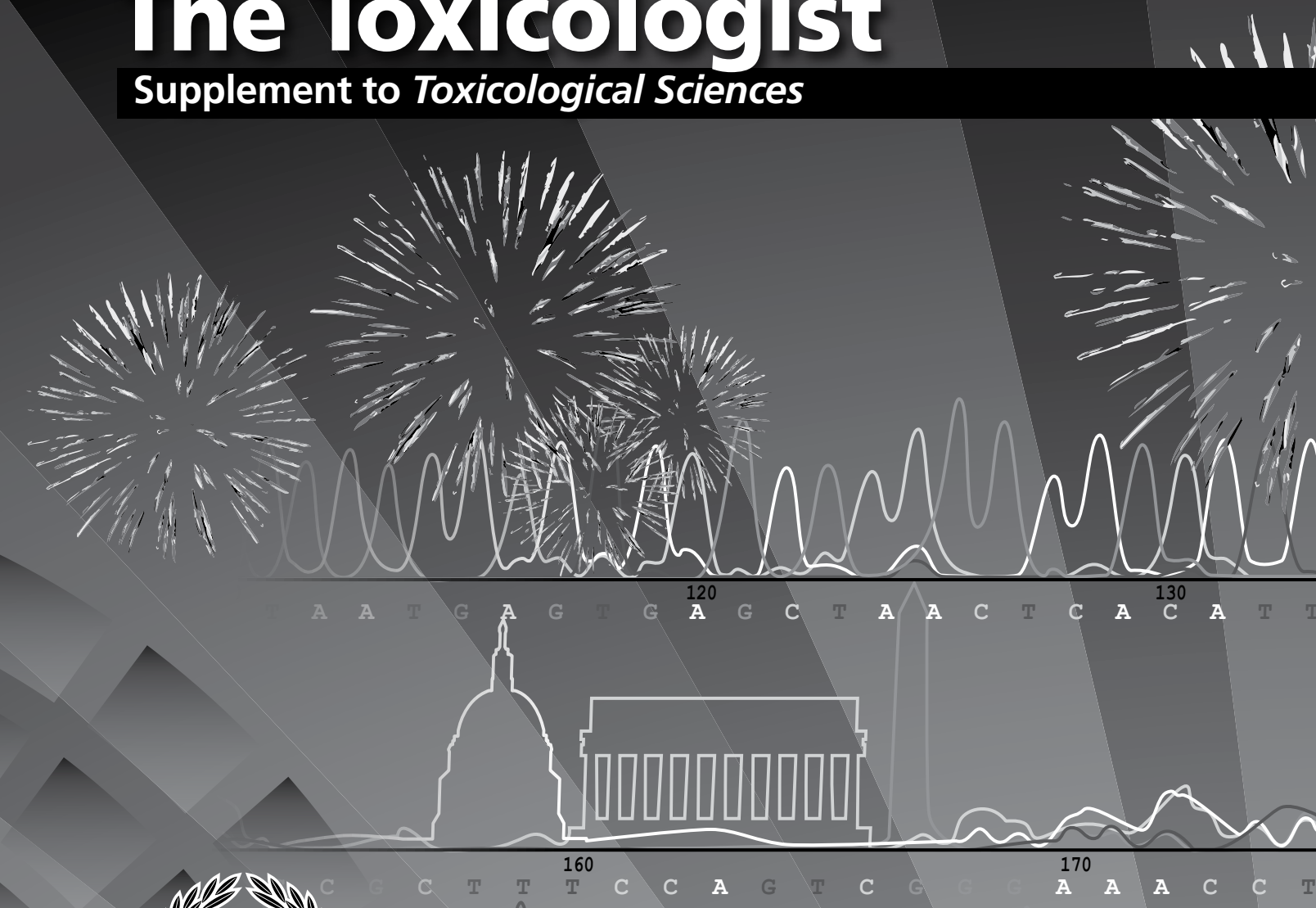

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

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

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