1749 Evaluating the Impact of Alternate Assumptions on Soil Remedial Levels Using US EPA's Integrated Exposure Uptake Biokinetic (IEUBK) Model

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In 2012, the CDC recommended that blood lead levels (BLLs) should be benchmarked to a reference value (RV), equal to the 97.5th percentile BLL from the National Health and Nutrition Evaluation Survey, rather than the 10 µg/dL "level of concern." The RV was 5 µg/dL in 2012. US EPA has not yet updated its Regional Screening Level (RSL) for soil lead to reflect the 2012 reference value, nor has it finalized revisions to other IEUBK inputs, although it has indicated it will do both. Use of the RV as the target BLL has important implications for managing exposures of children to lead. In this analysis, we evaluated the impact of different exposure assumptions for the soil lead RSL, assuming a target BLL of 5 µg/dL and a probability of an elevated BLL of 1 or 2%. We chose assumptions which may plausibly differ across sites or, as with the BLL geometric standard deviation (GSD), may differ at lower BLL distributions. Specifically, we varied the population BLL GSD, soil lead bioavailability, soil-dust transfer rate, and water lead concentrations. Depending upon the chosen assumptions, calculated soil lead RSLs varied several-fold, in some cases yielding RSLs below background soil lead levels for certain urban areas. We also evaluated uncertainty in quantifying the contribution of soil lead to BLL in the IEUBK model by comparing IEUBK model estimates to those based on statistical modeling from soil lead: blood lead epidemiology studies. This comparison indicated higher blood lead predictions with the IEUBK model than with the selected epidemiologically-based models. While this analysis identified important challenges for remedial decisions with use of the RV target, it also identified approaches for priority setting and areas for reducing uncertainty with additional information.

1750 Probabilistic Modeling of Childhood Multimedia Lead Exposures: Examining the Soil Ingestion Pathway

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This talk describes a multimedia probabilistic exposure modeling approach to guide public health decisions related to lead, achieved by coupling US EPA's SHEDS-Multimedia and IEUBK models. The goal of this effort was to advance a national-scale understanding of the relationship between lead concentrations in environmental media and blood lead levels (BLL) of infants and young children, with the purpose of determining what drinking water levels can keep children's blood lead levels below specified levels. Many factors play a role in lead exposure, including media concentrations, age-dependent media intake rates, lead bioavailability, and biological variability in lead uptake. Our probabilistic modeling approach incorporated distributional assumptions for each these factors, with the exception of bioavailability for which point estimates were applied. We observed good agreement in predicted childhood BLL (0-23% relative error) with nationally representative children's BLL, yet somewhat decreased agreement for a regional assessment (35-43% relative error). Pathway contribution analysis (national scale) revealed soil/dust ingestion was the dominant pathway for BLL above the 80% percentile among children 2 to <7 years of age, and suggests a high value of information for determinants of this pathway (lead soil and dust concentrations, soil/dust ingestion rates, and lead soil/dust bioavailability). While considerable work has been done to assess lead bioavailability (e.g., lead species, nutritional status), making use of this data in exposure modeling is constrained by the availability of pertinent exposure information. Herein we discuss these data needs with emphasis on identifying populations most at risk from lead exposure. *This abstract does not represent US EPA policy.*

1751 Nanotoxicology: State of the Science and the Path Forward

T. Thomas. *US Consumer Product Safety Commission, Rockville, MD.*

The US National Nanotechnology Initiative (NNI) was established in 2001 to support the responsible development of the emerging science of nanotechnology and bring together stakeholders from the federal government, industry, and academia. The goal was to thoroughly address the potential health and safety implications of nanomaterials. Stakeholders emphasized the complexity of nanotoxicology, the importance of understanding the novel physicochemical properties of nanomaterials, and how traditional toxicity testing strategies should be modified to address these unique properties. The toxicology community has responded to this call-to-action through the emergence of nanotoxicology as a subspecialty, including the 2008 launch of the SOT Nanotoxicology Specialty Section. Over the past 10 years, thousands of peer-reviewed studies have been published in journals, including those developed specifically for nanotoxicology, in addition to numerous meetings and symposia. Currently, the nanotoxicology community is at a critical juncture where stakeholders have begun to pose serious questions regarding the achievements of this new science. Concerns include the presentation and robustness of the data in published studies and whether standardized and validated methods were used. General questions surround whether available data meet critical data gaps, whether nanotoxicology should continue to exist as a subdiscipline of toxicology, and whether funding should be consolidated. The toxicology community should work in tandem with other disciplines that play a critical role in understanding the relative risks associated with nanomaterials. This session will bring together researchers and scientists from the federal government, industry, and academia to provide an overview of the lessons learned and the support provided to industry for commercializing nano-enabled products. The session will present carbon nanotube toxicity as a case study of the efforts to understand whether toxicity of engineered nanomaterial exposures is adequately understood. Other topics include the state of the science in terms of human health effects, the role of the NNI in assuring responsible development of nanotechnology, and the future directions of industries for incorporating nanotechnology. Lastly, the path forward for nanotoxicology, highlighting knowledge gaps and emerging research needs, will be presented, followed by an open discussion with the panel of speakers.

1752 State of the Science: Nanotoxicology of Carbon Nanotubes (CNTs)

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Carbon nanotube applications in structural materials, electronics, and medicine are expanding rapidly, leading to potential occupational exposures. Fifteen years ago, concern was raised that high aspect ratio durable CNTs may act as asbestos to cause pulmonary disease. Numerous studies have since shown that CNTs cause lung inflammation/damage, granulomas (due to CNT agglomerates), and fibrosis (due to deposition of smaller CNT structures in the distal lung). Although these pulmonary responses may be asbestos-like, CNT pathogenesis differs from asbestos; i.e., 1) asbestos causes frustrated phagocytosis and persistent inflammation, while CNTs do not; 2) purified CNTs do not generate radicals as does asbestos; and 3) lung gene expression pathways differ for MWCNTs vs. asbestos. Indeed, the fibrogenic potency of CNTs appears driven by their ability to enter the alveolar interstitium and directly activate fibroblast proliferation and collagen production. Fibrogenic potential is single-walled CNTs > multi-walled (MW)CNTs > carbon nanofibers = asbestos. Carboxylation of MWCNTs decreases fibrotic potency, while amination enhances bioactivity. These pulmonary responses to CNTs are qualitatively similar in mice vs. rats and quantitatively similar in males vs. females. Recent results also indicate that MWCNTs can both initiate and promote lung cancer, with male rats being more susceptible to MWCNT-induced lung tumors than female rats. MWCNTs can migrate to the interpleural space, and after two years of inhalation exposure MWCNT-induced mesothelial hyperplasia was reported. However, to date, no mesothelioma has been demonstrated following pulmonary exposure to MWCNTs. Pulmonary exposure to MWCNTs has also been reported to adversely affect cardiac performance and microvascular function. Lung sensory neurons in the lung are involved in this response. Therefore, recent expansion of nanotoxicology data allows for risk analysis for CNTs.

1753 State of the Science: Human Health Effects of Engineered Nanomaterials

M. Schubauer-Berigan. *NIOSH, Cincinnati, OH.* Sponsor: T. Thomas

Human (epidemiologic) studies of the health effects of engineered nanomaterials (ENM) have been few and generally confined to the materials expected to be most hazardous [e.g., carbon nanotubes (CNT) or nanofibers (CNF)] or in most common use (e.g., titanium dioxide). The occupational setting is currently the most appropriate for conducting health studies of ENM, given the low exposures and study feasibility challenges in the general population. Occupational studies are challenging, due to the small workforce sizes involved in ENM manufacturing and use, difficulty for researchers in accessing the populations, and problematic exposure assessment for most ENM; an emblematic example of the latter is uncertainty about which aspects of ENM exposure are most relevant to health. A recent review of epidemiologic studies of ENM identified 15 studies in progress (three-quarters of which were cross-sectional) of 9 unique populations of ENM workers. In addition, a relatively large cross-sectional study of US CNT and CNF workers has been completed and full publications of studies of other CNT workers have appeared in the literature. Relatively few overt health effects have been found to be

associated with CNT or CNF exposure in these epidemiologic studies. The exposures in the human studies are generally lower than those used in most toxicology studies, which hampers their comparability. Most published studies have reported some inflammatory or other biomarkers to be associated with measured exposures to ENM, although specific findings tend to be inconsistent across populations. These and other challenges in conducting epidemiologic research of ENM point to the need to pool data across studies and populations. This will require study coordination to ensure comparability of exposure and outcome measurement.

1754 Ensuring Responsible Development of Nanotechnology

L. Friedersdorf. *National Nanotechnology Coordination Office (NNCO), Arlington, VA.*

From the very inception of the US National Nanotechnology Initiative (NNI), responsible development of nanotechnology has been one of its primary goals. Responsible development encompasses support for the creation of knowledge for the evaluation of the potential risks and benefits of nanotechnology to the environment and human health and safety; timely dissemination, evaluation, and incorporation of this knowledge; consideration of ethical, legal, and societal implications; and incorporation of sustainability principles. This presentation will provide an overview of the role the NNI has played in addressing this goal. Mechanisms employed to promote active discussion about nanotechnology-related environmental, health, and safety research and to leverage knowledge and resources internationally will also be discussed.

1755 An Industry Perspective on the Federal Role in Nanotoxicology

S. Clancy. *Evonik, Parsippany, NJ.*

Industry has been an active participant in the field of nanotechnology for many years. In fact, industry's involvement precedes the use of the term "nanotechnology," through the production and use of materials described by terms such as "ultrafine," that we may describe as nanomaterials today. Along the way, the industry community has also taken steps to ensure the responsible development and use of nanomaterials, which has often included considering important matters such as characterization and toxicology. The US Federal government has played an important role in helping to establish more common approaches to these issues including more common terminology, metrology, and EHS practices. These improvements have facilitated the development of new materials and increased the confidence in the safe use of legacy nanomaterials. This presentation will feature examples of how the contributions from the Federal government have supported these activities and suggest opportunities for additional contributions.

1756 Nanotoxicology and the Path Forward

A. Elder. *University of Rochester, Rochester, NY.*

As the field of nanotoxicology is growing into maturity, there is a need to reflect on the research findings of the last several years to inform decisions regarding future efforts, keeping a clear focus on delivering the critical information that will ensure safer and sustainable development of new technologies. Many important toxicological and human health concepts will be highlighted in this session that have been derived through carefully-planned, collaborative, and coordinated research efforts. A similar approach should be followed going forward, even if the focus shifts to fill knowledge gaps in different areas. One need for the future is to expand the epidemiological database. There are very few workplace exposure monitoring campaigns or health effects studies going on in exposed occupational cohorts, so attention should be devoted to filling this gap so that the wealth of *in vitro* and animal *in vivo* studies can be placed into proper context. The use of modern exposure characterization methodology is of critical importance. In these efforts, a focus on the entire product life cycle is necessary. Secondly, attention should be devoted to validating findings from *in vitro* models with respect to the *in vivo* experience on the dosimetric and mechanistic levels. Since much of the current literature focuses on effects following acute exposures, there is room for significant advancement in knowledge regarding the fate and effects of ENMs upon subchronic through chronic exposure. In addition, very little is understood about the effects of ENMs in susceptible or vulnerable populations. Lastly, modern applications of nanotechnology have moved beyond the primary nanoparticle, so toxicological and workplace/environmental sampling studies should be designed to reflect more complex materials.

1757 An *In Vivo* Model for the Simultaneous Assessment of Cardiovascular, Neuromuscular, and/or Central Liabilities of Oximes: Establishing 2PAM Liabilities and Mode-of-Death

S. Roof, R. Hamlin, and C. del Rio. *QTest Labs, Columbus, OH.* Sponsor: R. Hamlin

Pralidoxime (2PAM) is a clinical-stage field-ready oxime utilized as a cholinesterase reactivator. Due to its multiple on/off target actions, as well as to the tight interactions between cardiovascular, neuro-muscular, and respiratory centers, establishing its specific liabilities *in vivo* remains difficult. In this study, the simultaneous dose-response(s) of 2PAM on neuro-muscular and cardiovascular end-points were evaluated *in vivo*, in an effort to establish specific *in vivo* liabilities. Ten anesthetized (2.5% isoflurane) and mechanically-ventilated male Sprague Dawley rats were instrumented to simultaneously assess systemic/left ventricular hemodynamics as well as skeletal and diaphragmatic function in order to differentiate between central and direct junctional effects, diaphragmatic function was studied in both intact (n = 5, centrally driven) as well as de-centralized preparations (n = 5) where the phrenic nerve was transected cranially and electrically stimulated (4V for 10 ms at 0.2 Hz). In all cases, data were collected before and during 2PAM Administration (2.5 mg/kg/min IV) for 2 hours. 2PAM treatment dose dependently depressed skeletal and diaphragmatic muscle function. Both stimulated (femoral nerve) skeletal muscle and intact (centrally-driven) diaphragmatic twitches followed comparable time-courses, declining 50% (IC_{50}) and 90% from baseline (IC_{90}) at cumulative 2PAM doses of ~80 and ~160 mg/kg (respectively). Alternatively, stimulated (de-centralized) diaphragmatic function was more resistant to inhibition (IC_{50}:180 mg/kg, IC_{90}: 250 mg/kg), suggesting both a direct and a central action of 2PAM. In all cases, administration of 2PAM resulted in slight vasopression (+14 ± 3 mmHg) and in an early positive chronotropic effect (+11-20 ± 3 bpm). Taken together, these data support diaphragmatic/respiratory depression as the primary liability of 2PAM *in vivo* (likely resulting in death via hypoventilation/asphyxia), as 2PAM lacked detrimental cardiovascular effects at the exposures studied. In addition, the results also suggest both that 1) 2PAM may directly alter central/afferent respiratory pathways and 2) skeletal muscle function may provide premonitory insights into the diaphragmatic inhibition of oximes. Overall, this study demonstrates that the potential neuro-muscular, cardiovascular, and respiratory *in vivo* liabilities of oximes can be simultaneously assessed pre-clinically.

1758 Evaluation of Agonists for the A1 Adenosine Receptor as Novel Anticonvulsant Medical Countermeasures to Soman (GD) Nerve Agent Intoxication

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Current medical countermeasures often have limited efficacy in suppressing seizure activity after organophosphorus nerve agent (NA) intoxication. Toward developing a more effective anticonvulsant treatment, we have shown that stimulation of the A1 adenosine (ADO) receptor (A1AR) with the agonist N6-cyclopentaladenosine (CPA) effectively prevents NA seizure. However, CPA at the effective dose (60 mg/kg) produces unwanted side effects e.g., prolonged sedation. This study aimed to determine if efficacy could be achieved at lower CPA doses, and to also determine if other agonists could potentially prevent seizure with fewer side effects. To do so, Sprague Dawley rats were surgically prepared for recording brain electroencephalographic (EEG) activity. One week later, rats received HI-6 (125 mg/kg, IP) and atropine methyl nitrate (2 mg/kg, IM) to prevent peripheral cholinergic symptoms and, thus, promote survival without affecting central activity. Rats were exposed to GD (1.6 x LD50, SC) or control vehicle 30 min later. One minute after GD, rats were treated IP with one of the following agonists at increasing dose levels until anti-seizure efficacy was achieved: CPA, 2-Chloro-N6-cyclopentyladenosine (CCPA), and (±)-5′-Chloro-5′-deoxy-ENBA (ENBA). Rats were prepared for neurohistopathological scoring 24 hrs later (0=no damage, 16=most severe). All A1AR agonists were efficacious in preventing seizure and promoting survival. The effective doses for the A1AR agonists were: 60 mg/kg CPA, 36 mg/kg CCPA, and 62 mg/kg ENBA. Whereas saline-treated rats experienced 100% seizure and 21% survival (N=28), ADO treatments reduced seizure occurrence and improved survival rates: 8% seizure and 83% survival with CPA (60 mg/kg, N=12), 17% seizure and 75% survival with CCPA (36 mg/kg, N=12), and 8% seizure, 83% survival with ENBA (62 mg/kg, N=12). ADO also suppressed neuropathology: saline-treated rats had severe brain

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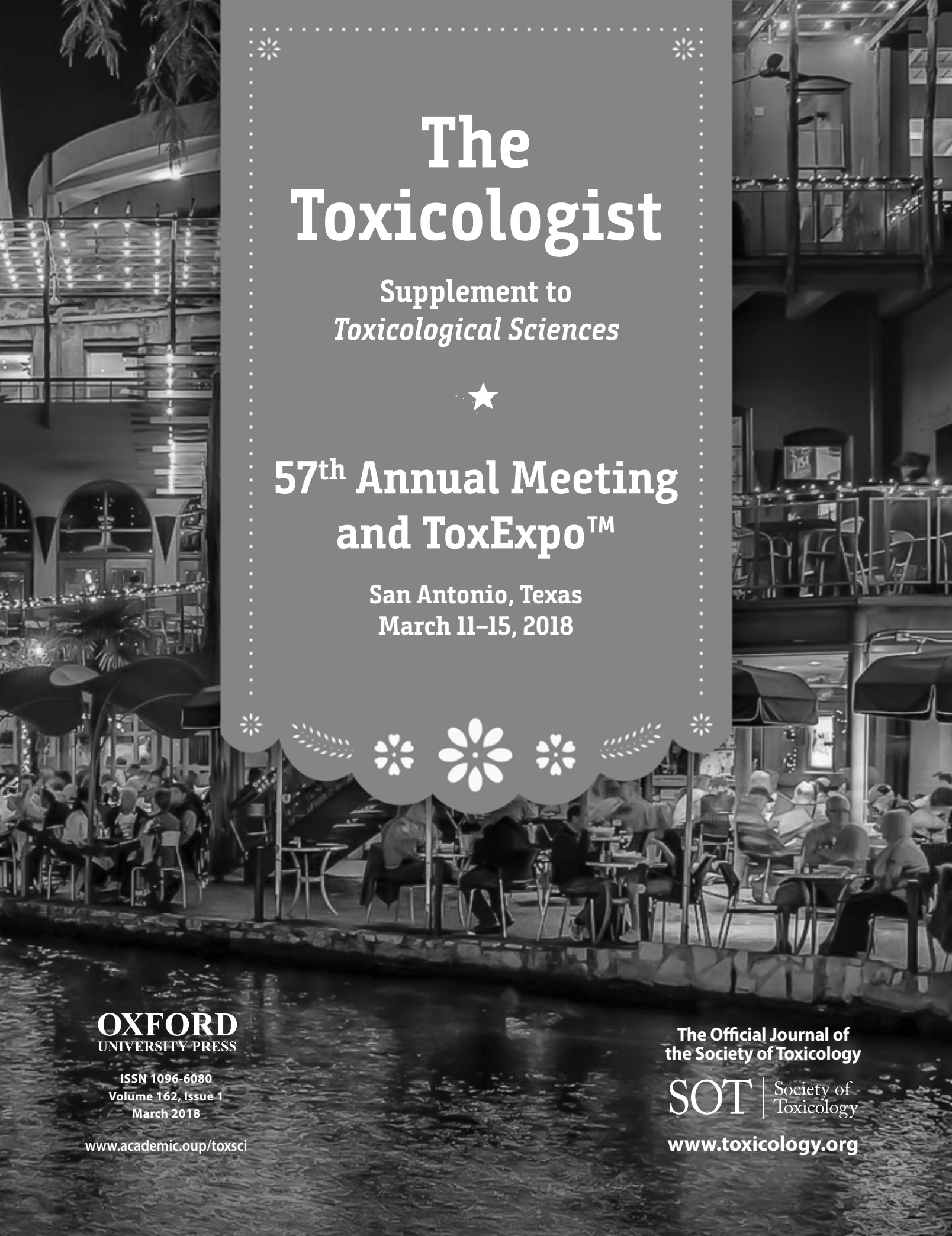

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