An International Journal Specializing in Environmental Mutagenesis

Volume 52
Number S1
October 2011

EMS Abstracts

Supplement to *Environmental and Molecular Mutagenesis*

In this issue: Abstracts from the Environmental Mutagen Society 42nd Annual Meeting, October 15–19, 2011, Montréal, Québec, Canada
Program Chair: Catherine B. Klein

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Environmental and Molecular Mutagenesis

JOURNAL OF THE ENVIRONMENTAL MUTAGEN SOCIETY

ENVIRONMENTAL AND MOLECULAR MUTAGENESIS (Print ISSN 0893-6692; Online ISSN 1098-2280 at Wiley Online Library, www.wileyonlinelibrary.com) is published monthly in January, March, April, May, June, July, August, October, December by Wiley-Liss, Inc., through Wiley Subscription Services, Inc., a Wiley Company, 111 River Street, Hoboken, NJ 07030. **Postmaster:** Send address changes to **ENVIRONMENTAL AND MOLECULAR MUTAGENESIS,** Journal Customer Services, John Wiley & Sons Inc., 350 Main St., Malden, MA 02148-5020. **Send subscription inquiries** *c/o* John Wiley & Sons, Inc., Attn: Journals Admin Dept UK, 111 River Street, Hoboken, NJ 07030, (201) 748-6645.
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Volume 52, Number S1 ..... **2011**

Volume 52, Number S1, was posted the week of October 3, 2011.

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Environmental Mutagen Society 42nd Annual Meeting

Environmental Impacts on the Genome and Epigenome: Mechanisms and Risks

October 15–19, 2011

Hilton Montréal Bonaventure Montréal, Québec, Canada

Program Chair: Catherine B. Klein, Ph.D.

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S58

Preventing Occupational Exposures to Antineoplastic Drugs in Health Care Settings. Connor TH. National Institute for Occupational Safety and Health, Cincinnati, OH, United States.

Introduction: Occupational exposure to antineoplastic drugs has been a concern of healthcare professionals since the 1970s following reports of secondary cancers in patients treated with these drugs. The detection of mutagens in the urine of nurses first alerted healthcare professionals to the potential for exposure to antineoplastic drugs in the workplace. Since many of the anti-cancer drugs cause DNA damage, properly designed tests for genotoxicity can reflect exposure to these drugs. Methods: Peer-reviewed articles dealing with biomarkers of genotoxic damage associated with occupational exposure to antineoplastic drugs published between 1990 and 2011 were reviewed. The studies employed various types of assays for biomarkers of genotoxicity. In addition to urine mutagenicity, biomarkers included chromosomal aberrations, sister chromatid exchanges, induction of micronuclei and DNA damage, plus several miscellaneous endpoints. Results: During this period, 99 studies were identified that evaluated differences in biomarkers of genotoxic damage in healthcare workers as compared to matched control groups. The majority of the studies was cross-sectional in design and often had the limitation of small sample size. Some studies evaluated interventions aimed at reducing exposure to these drugs. Approximately two-thirds of the studies reported an association between occupational exposure to antineoplastic drugs and the biomarker of genotoxicity. In most studies, interventions reduced the frequency of genotoxic damage. Discussion: Although the long-term consequences of the exposure to antineoplastic drugs are not fully understood, given their genotoxic potential, efforts should be undertaken to reduce potential exposure to these drugs in the workplace.

Symposium 13–Using DNA Adducts in Risk Assessment: Approaches, Considerations, and Significance

S59

ILSI/HESI DNA Adducts Project Committee: Review of Case Study Outcomes: Tamoxifen, AFB_1, and VCl. Pottenger LH. The Dow Chemical Company, Midland, MI, United States.

The biological significance and role of DNA adduct data in risk assessment are debated. An ILSI/HESI Committee published a systematic approach for the evaluation of DNA adduct data in a key event dose-response framework for a mutagenic mode-of-action (MOA) analysis for cancer risk. The approach stresses the need to create a context for adduct data in conjunction with other key types of data such as dosimetry, mechanistic response data, and tumor incidence. This systematic approach was applied to data for three chemicals to illustrate its use: aflatoxin B_1, tamoxifen, and vinyl chloride. These chemicals presented a variety of characteristics and some specific challenges for adduct data interpretation, such as presence of background/endogenous adducts, different MOAs for rodents *vs.* humans, and data quality and reliability. Analysis of these case studies led to a set of general principles for evaluating the role of DNA adduct data in the MOA, including the following: Target tissue and adduct type depend on exposure concentration, duration, and internal dose determinants such as physico-chemical properties, anatomical and physiological factors, and ADME processes. Adduct profiles can change with duration or dose, due to differences in repair/persistence of specific adducts. Both characterization and structural identification are necessary for DNA adduct use in MOA assessment. Key conclusions include the following: DNA adduct data cannot be used in isolation to determine a mutagenic MOA; DNA adducts represent biomarkers of exposure and not of effect; and DNA adduct data alone are informative but not sufficient to assign a mutagenic MOA.

S60

Application of a Decsion Analytic Approach to Case Studies. Jarabek AM. U.S. EPA, National Center for Environmental Assessment, Research Triangle Park, NC, United States.

Recent assessment approaches use weight of evidence and human relevance frameworks to evaluate evidence on the mode of action (MOA) for a chemical. To date, what is often lacking is an explicit expression of data quality, utility, and reliability to support claims of causality for a given key event(s). This expression is important because judgments concerning data on parameters for specific steps influence the confidence in the ultimate decision regarding causality. A two-step decision analytic approach to evaluate causality is proposed. The 1st step is to populate a conceptual MOA model with specific data on parameters. Description of the pathogenesis process is divided into characterization of two key components: dosimetry (toxicokinetics) and response (toxicodynamics). The 2nd step entails evaluating both the ability of the data to describe or represent the particular parameter or process, and the extrapolation premises or assumptions required to apply these data to the human disease target context. This requires explicit evaluation of the data from various observational contexts: *in vitro*, *in vivo* laboratory animal and human studies. Data are assigned to evidence categories (direct empirical, semi-empirical, empirical correlation or theory-based inference) to assess relevance. Coherence of data within an observational context and then across contexts is used to arrive at a summary judgment of causality for each of the two characterizations. These are combined to arrive at overall confidence in the conclusion regarding the causal role of the proposed key event(s). (These views are those of the author and do not represent U.S. EPA policy).

S61

Mutagenesis and Repair of O^6- and N7-Alkylguanine DNA Adducts. Fuchs RP[1], Mazon G[1], Modesti M[1], Phillipin G[1], Gasparutto D[2], Cadet J[2]. [1]CNRS, UPR 3081, Marseille, France, [2]CEA, LAN, Grenoble, France.

The mutagenicity of O^6- and N7-alkylguanine adducts formed by ethylene oxide (EO) and propylene oxide (PO) was investigated by the use of single-adducted plasmids. N7-alkylguanine adducts were found to be intrinsically non-mutagenic provided the apurinic sites that may form spontaneously are removed prior to introduction of the plasmids into cells. In contrast, O^6-alkylG adducts are highly mutagenic due to their capacity to efficiently mispair with T during replication, triggering G->A transitions. For these lesions, mutagenesis is largely prevented by repair strategies *via* alkyltransferases (AT) or Nucleotide Excision Repair (NER) pathways. Recently, we have shown that the alkyltransferase-like gene ybaZ (eATL) enhances repair of these adducts by Nucleotide Excision Repair. In addition, methyl-directed Mismatch Repair (MMR) is known to trigger sensitivity to methylating agents *via* a mechanism that involves recognition by MutS of the O^6-mG:T replication intermediates. We show that eATL prevents MMR-mediated attack of the O^6-alkylG:T replication intermediate for the larger alkyl groups but not for methyl. *In vivo* data are compatible with the occurrence of repeated cycles of MMR attack of the O^6-alkylG:T intermediate. *In vitro*, the eATL protein efficiently prevents binding of MutS to the O^6-alkylG:T mispairs formed by the larger alkyl groups but not by methyl. In conclusion, eATL not only enhances the efficiency of repair of these larger, O^6-alkylG adducts by NER, but it also shields these adducts from MMR-mediated toxicity. This is the first report demonstrating the lack of intrinsic mutagenic effect by N7-alkylG adducts induced by EO or PO.