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

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S54

Dose-Response Issues in the Regulation of Chemicals. Schoeny RS. U.S. EPA Office of Water, Washington DC, United States.

U.S. EPA and other regulatory groups often define "science policies" as a means of moving forward with risk assessments and management decisions in the absence of all the data these bodies would prefer to have. These science policies may include the use of default assumptions, values and methodologies. Parameters for development and use of science policies have been published in Agency Guidelines as well as in reports by the U.S. National Academies of Sciences such as Science and Judgment and the more recent Science and Decisions (the Silver Book). The U.S. EPA 2005 Cancer Guidelines stated a preference for use of data over defaults and mode of action (MOA) as a basis for key risk judgments; regulatory groups in Europe and elsewhere express similar preference. Furthermore the Cancer Guidelines gives the highest priority to use of biologically based dose-response models (BBDR), when supported by data, over use of any default. A BBDR is preferred to default, linear, low-dose extrapolation from a point of departure for carcinogens thought to act through a mutagenic MOA. It is noted that risk assessment is only one input to the process whereby choices among risk management options are made. Policy (other than science policy and in some instances defined in statute) is a major factor in this decision process. Examples of use of policy based on science *vs.* science policy will be presented. The opinions in this abstract are those of the author and may not reflect policies of U.S. EPA.

Symposium 12–Risks Associated with Inadvertent Exposures to Pharmaceutical and Prescription Drugs

S55

Inadvertent Exposures to Pharmaceutical Drugs: Overview. Weston A. NIOSH, Morgantown, WV, United States.

Inadvertent exposure to pharmaceutical drugs can occur through multiple routes (drug development and manufacturing worker exposure/pharmacist exposure/healthcare worker exposure/patient exposure), several of which will be explored during this symposium. The first presentation will address research/development and manufacturing worker exposures, where risk assessment may be based on chemical structure, and comparisons made with known, structurally similar drugs. Also relevant to this is the use of equipment in the context of synthesis of a previous drug, where residual materials may contaminate a subsequent preparation. Therefore Risk-based Manufacture of Pharmaceutical Products is an important consideration. The second presentation will consider patient safety in the context of such residual contamination of pharmaceutical products. Specifically, the acceptable level for genotoxic impurities occurring during drug synthesis, the threshold for toxicological concern, and acceptable daily exposure will be explored. the third presentation will consider exposures to healthcare workers, especially in the context of antineoplastic drugs. The presence of antineoplastic drugs and their metabolites in the urine of nurses and other healthcare professionals confirms exposure. in each of these three exposure scenarios, pharmaceutical agents can cause genotoxic and/or mutagenic damage. Studies of workers and patients inadvertently exposed to pharmaceutical agents have included testing of surrogate tissues (peripheral white blood cells and buccal cells) for DNA damage; *in vitro* mutagenicity testing of urine has also been used as a marker of exposure. These and other testing measures have been employed to assess the efficacy of engineering controls and personal protective equipment to prevent inadvertent exposures.

S56

Risk-Based Manufacture of Pharmaceutical Products. Mahadevan B. Abbott Laboratories, Abbott Park, IL, United States.

The global pharmaceutical industry and regulators are responding to the challenge of significantly improving the way drug development and manufacturing is managed. In this regard, the use of the health-based limits as the basis for risk assessment in the manufacture of pharmaceutical products is a scientifically sound approach. Risk-MaPP (Risk-based Manufacture of Pharmaceutical Products), an ISPE (International Society of Pharmaceutical Engineering) guidance document provides good practices that can help a company develop an approach that is effective, cost-efficient, and in compliance with existing regulations and related guidance. In this presentation, the concept of Risk-MaPP will be elaborated with particular emphasis on deriving an Acceptable Daily Exposure (ADE) for pharmaceuticals. The application of the Threshold of Toxicological Concern (TTC) concept to pharmaceutical manufacturing operations will also be illuminated with examples.

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Considerations for Risk Assessments of Genotoxic or Carcinogenic Impurities in Industry. Nicolette J. Abbott Laboratories, Abbott Park, IL, United States.

Pharmaceuticals are tested for their potential to cause genetic damage prior to being tested for safety and/or efficacy in clinical trials. Drugs that test positive in *in vitro* genetox studies are vetted in multiple *in vivo* and mechanistic studies prior to administration to volunteers in first in human trials. To make a synthetic compound, reactive starting materials and intermediates used in the route. Solvents and reagents can combine with these or together creating unwanted impurities in the final active pharmaceutical ingredient (API). These impurities themselves could have genotoxic potential. Historically, impurities in the API did not have to be identified unless they exceeded 0.1%, and qualification wasn't required unless above 0.15% in the API. In addition, these guidelines applied to the final marketed drug, with no guidance for drugs in clinical development. Unlike other toxicities, mutagenicity has been considered a non-thresholded phenomenon. To protect clinical trial subjects, recent guidance from the European Medicines Agency (EMEA) suggested that a 1.5 microgram per day or lower intake of genotoxic carcinogens would result in less than 1 additional cancer per 100,000 and that this is an acceptable level for genotoxic impurities found in a synthetic route. This is known as the threshold for toxicological concern or TTC for pharmaceuticals. Additional refinement has been made to account for short duration exposures in clinical trials without addition risk to the subject. This presentation will discuss evaluation of synthetic routes with emphasis application of the TTC as well as the staged-approach along with examples.