Editorial

ECETOC – EEMS Symposium on Dose-Response and Threshold-Mediated Mechanisms in Mutagenesis (Salzburg, Austria; 7 September 1998)

General introduction

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The symposium on "dose response and threshold effects in mutagenesis" co-sponsored by the European Environmental Mutagenesis Society (EEMS) and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) was held in Salzburg, Austria on September 7, 1998.

The recognition for the need for a symposium addressing threshold-mediated mechanisms in chemical mutagenesis began with an ECETOC task force on chemically induced aneuploidy. The Task Force work resulted in an ECETOC monograph in 1997 [1], and was published subsequently in a special issue of Mutation Research [2].

In its evaluation, the task force examined the significance of aneuploidy in human disease, the methods for detecting aneugens, the mechanisms by which aneugens exert their action and how aneugens, as mutagens, are evaluated by regulatory authorities worldwide. Recommendations for the testing of aneugens and for risk characterisation of chemicals with aneugenic potential were made. It was noted that for at least one class of aneugens, inhibitors of spindle function, which exert their action through mechanisms not involving direct interaction with DNA, thresholds can be, or have been, demonstrated [3,4]. In mutagen risk characterisation, particularly with hazard determination, the focus is primarily on the potential of substances to induce heritable mutations in man essentially with no particular consideration for the mechanisms by which mutations are induced. The target of concern is the human germ cell. Effects of mutagens on somatic cells are critical to the carcinogen risk characterisation process, and to the possibility that mutagens with demonstrated effects in somatic cells may cause similar effects in germ cells.

To ensure that hazard identification for aneugens is appropriately addressed, the Task Force made several proposals including the modification of mutagen classification schemes to take into account consideration of non-DNA reaction mechanisms. For quantitative risk assessment, the incorporation of mechanistic information and identification of critical targets (DNA and non-DNA), and establishing a dose-response relationship with defined no effect levels (thresholds) are critical. However, it was realised that this issue should address all mutagens and events in the mutagenic process for which thresholds can be determined, not only for aneugens.

This was the purpose of the Salzburg symposium. Appropriately is opened with the Paracelsus lecture presented by Professor H. Dopsch of the University of Salzburg on the 16th Century Austrian physician Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus; the title of his talks was "Poison or Remedy – Paracelsus and Pharmacotoxicology".

The symposium consisted of three sessions, the first overviewing the general concepts of thresholds for carcinogenesis and mutagenesis. In the first session, general concepts of thresholds in carcinogenesis and mutagenesis were reviewed. In Session 2, authors were asked to overview the current status of our knowledge, and were appropriate, present original studies which investigated the factors which may influence the shape of the dose-response curve. The third section integrated current methods and potential techniques which may be used to interpret dose-response curves and how they may be used in the

evaluation and validation of threshold mechanisms for individual chemicals.

It was clear from Session 1 to 3 and the papers presented here that we are still some way from having the appropriate experimental data to provide mechanistic answers to the questions of the shape of the dose-response curve and the role of modifying factors for many chemicals. Thus, in this issue, we have attempted to illustrate future research needs and current deficiencies in our understanding of how to adequately decide on the relevance of threshold-mediated toxicity mechanisms in focusing our priorities for chemical recognition.

References

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