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MUT/04/14

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Genotoxic Carcinogens and DNA repair at low doses

Introduction

1. The COM had been asked by COC to provide advice regarding an approach to evaluating the significance of DNA repair induction at low doses of genotoxic carcinogens in the context of the hormesis hypothesis. Members discussed the information presented in a short introductory paper (MUT/04/3) and agreed it would be useful to carry out a literature search targeted on low dose effects of a few direct acting chemical mutagens on DNA adduct formation, mutation rates, and the significance of DNA repair mechanisms. The search should concentrate on low molecular weight compounds such as ethylene oxide and ethyl or methyl methanesulphonate, for which there was a rich database. Members agreed that bacteria would most likely demonstrate the most sensitivity to low doses of mutagens and had reservations as to whether mammalian cell systems would have sufficient sensitivity to detect evidence for an effect of DNA repair induction on the dose-response relationship for mutation.
2. The Committee considered that natural variability would make the detection of any 'U' shaped curve very difficult. It would however be prudent to consider the implications with regard to thresholds and the current COM policy to make the prudent assumption of the absence of thresholds for clear in-vivo mutagens.
3. The DH Toxicology Unit have prepared a review where the literature search focused on the low molecular weight compounds N-nitroso-N'-methyl-N-nitrosoguanidine (MNNG), ethyl methane sulphonate (EMS) and methyl methane sulphonate (MMS) and a series of papers were singled out and reviewed (Annex 1). This includes evaluation of O⁶-methyl transferases (O⁶MT) in bacterial and mammalian cell systems (a DNA repair pathway known to be induced by mutagens which gives rise to response thresholds) and a limited number of other or unspecified DNA repair mechanisms.

Questions arising from DH Toxicology Unit review

4. Members are asked to consider the discussion points and questions posed in the DH Toxicology Unit paper and to advise whether any

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additional evaluation is needed by COM before providing advice to COC, and if so, what further work should be undertaken.

- i) Do the data for O6-MT induction suggest threshold or hormesis type dose response curves could occur *in vivo*?
- ii) Are there sufficient data to draw a conclusion with regards to the relevance of other DNA repair mechanisms in relation to the hormesis concept?
- iii) Should any further work be undertaken before final conclusions can be drawn ?
- iv) Do these data provide any evidence to warrant reconsideration of the Committees advice regarding the prudent assumption that these alkylating agents do not have a threshold. with respect to their mutagenic effects?

Secretariat May 2004.