

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Accelerator mass spectrometry - an aid to carcinogen risk assessment

Introduction

1. Accelerator Mass Spectrometry (AMS) is the most sensitive technique for measuring the formation of adducts with DNA. AMS technology allows the accurate measurement of very low levels of radiolabelled chemicals (particularly ^{14}C) in biological samples at around 10^{-21} to 10^{-18} mole. The Committee was asked to consider the value of AMS for the assessment of chemically induced carcinogenicity.

Overview of method

2. The Committee noted that high levels of sensitivity and reproducibility in the analysis of biological samples were reported with AMS (1,2,3). The sensitivity of the technique was related to the background level of radioactivity in the sample and, if individual adducts are being investigated, the quality and effectiveness of the HPLC separation used in the sample preparations. However, the cost of AMS technology is very high

Applications of AMS for the assessment of chemically induced carcinogenicity

3. The COC reviewed literature on AMS and noted that data obtained from this technology was suitable for hazard characterisation, providing data on tissue levels of chemical carcinogens and mechanistic information for risk assessment.

4. Hazard Characterisation: AMS provides a tool for the detection and quantification of very low levels of DNA adducts with a high degree of sensitivity. However, the COC noted that the interpretation of DNA adduct data provided by AMS can be particularly difficult (e.g. the exclusion on non-specific binding) as AMS merely provides an accurate measurement of the relative amounts of one isotope in a biological sample compared to another. The biological significance of very low levels of binding is difficult to assess. Thus, additional techniques and expert judgement are required to evaluate the structure and relevance of any adducts detected by AMS.

5. Tissue Levels of Carcinogens: AMS provides a tool for quantifying exposure and uptake of carcinogens at environmental exposure levels. Studies conducted using AMS in animals and human volunteers following exposure to low levels of the food process contaminants MeIQx and PhIP (known rodent carcinogens),

demonstrated that MeIQx and PhIP bound to DNA in human colon tissue at dietary exposure levels (4,5,6,7). However, no conclusions could be drawn on the significance of the DNA adducts detected. In addition, AMS provided toxicokinetic data at relevant dose levels and allowed for a comparison of interspecies differences in metabolism and bioactivation of MeIQx and PhIP in target tissues (8,9,10,6). The value of AMS for the conduct of ADME studies at relevant dose levels, particularly kinetic and metabolism studies for pharmaceuticals was noted.

6. The Committee noted that a limitation of AMS technology in humans was the need to administer radiolabelled carcinogens, although very low radiological dose levels (approximately 1/10th of the natural radiological dose received by adults each day) can be used. The Committee indicated that the development of post-labelling methods would make a significant improvement in the utility of AMS, provided the sensitivity of the method could be maintained.

7. Mechanistic information: AMS has the potential to provide valuable information for risk assessment for chemical carcinogens. Thus, AMS enabled comparison of the levels of DNA binding reported with tamoxifen in various tissues and organs of laboratory animals and also comparison of such data to similar studies in humans at therapeutic dose levels (11). The studies with human volunteers confirmed the results of previous ³²P post-labelling experiments and demonstrated that tamoxifen induced low levels of DNA binding in the uterus of women administered therapeutic dose levels before surgery (12). However, no conclusions could be drawn with regard to the significance of the low levels of DNA binding detected by AMS to the development of endometrial cancers in women. AMS studies with tamoxifen and its analogue toremifene also highlighted its applicability for SAR assessments (13,11). Thus, considerably lower levels of DNA binding were reported with toremifene compared to tamoxifen in the liver and reproductive tract of rats following administration of equivalent dose levels.

8. In a separate study, the lack of DNA binding in the urinary bladder of male rats administered the pesticide ortho-phenylphenol provided convincing evidence to suggest a non-genotoxic mechanism of carcinogenicity (14) with respect to bladder tumours seen in male rats in life time bioassays (15,16).

Overall conclusion

9. AMS is highly sensitive and reproducible technique. Its main uses in the area of chemical carcinogenicity are for hazard characterisation, measurement of tissue levels of administered radiolabelled compounds and mechanistic investigations. However, the biological significance of the very low levels of binding that may be observed is difficult to assess. Furthermore, the very high cost of the technology currently limits the use of AMS.

COC

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