

Interpretation of margins of exposure for genotoxic carcinogens

Area of research interest: [Chemical hazards in food and feed](#)

Study duration: 2010-01-01

Project code: FS231016 (T01051)

Conducted by: Imperial College London - Experimental Medicine and Toxicology, Division of Investigative Science and The Food and Environment Research Agency (FERA)

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Background

In the UK and the rest of Europe, the general approach for assessing the risks from genotoxic carcinogens has been to reduce exposure to levels that are 'as low as reasonably achievable' (ALARA), because it is not possible to identify an intake without a risk. However, this approach does not provide a clear basis for deciding on the urgency or extent of risk management actions.

To assess the risks from genotoxic carcinogens, EU and international scientific committees have been using the margin of exposure (MOE) approach, which compares estimated exposure to a selected benchmark dose lower confidence limit (BMDL). The MOE approach is used in risk assessment to determine the level of risk to those exposed, for substances which are both genotoxic and carcinogenic, and consequently where it is not possible to identify an intake without a risk. The MOE approach assesses the level of concern. The aim of this study was to develop a robust scientific rationale for defining levels of concern associated with given values or ranges of MOE for genotoxic carcinogens.

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Research Approach

First, a systematic review of existing proposals for a level of concern and alternative approaches for interpreting MOE was conducted. A second review examined the state of knowledge for how assessment factors should be combined in risk assessment. Additionally, two expert elicitation exercises were undertaken: the first to gather expert opinion on low-dose extrapolation for genotoxic carcinogens in general, and the second focusing on four selected examples: aflatoxin B1, benzo[a]pyrene, ethylmethanesulfonate and ethylnitrosourea. A statistical framework was developed for combining assessment factors to account for different sources of uncertainty and variability when interpreting the MOE. A major part of the project examined the relationship between MOEs and human cancers directly, by comparing risk estimates obtained from carcinogenicity data in experimental animals, using the MOE approach, with the measured risk in exposed subjects, obtained from epidemiological studies. The final stage of the project integrated the different lines of considered evidence, to derive overall conclusions on the level of concern associated with an MOE of 10,000. That is, if the BMDL10 value of 170 ng/kg bw/day for aflatoxin B1 was divided by an estimated human exposure value of 0.017 ng aflatoxin B/kg bw/day, the MOE value would be 10,000.

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Results

The overall conclusion of the research project was that it is not possible to establish with certainty the level of concern for a MOE of 10,000. Some of the case studies indicated that an MOE of 10,000 is a low concern, whereas for others the uncertainties in the assessments were such that conclusions could not be drawn. The independent Committee on Carcinogenicity (COC) agreed that on the basis of the outcomes of this project there was no need to alter the previous conclusions on the MOE approach where MOEs less than 10,000 were considered to be of possible concern, those between 10,000 – 1,000,000 were considered unlikely to be of concern and those above 1,000,000 were considered highly unlikely to be of concern. The COC encouraged further studies addressing the mode of action in order to infer the shape of the dose response relationship at low doses which might support developments in the MOE approach.

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Published Papers

1. Boobis A, Flari V, Gosling JP, Hart A, Craig P, Rushton L, Idahosa-Taylor E. 2013. Interpretation of the margin of exposure for genotoxic carcinogens – Elicitation of expert knowledge about the form of the dose response curve at human relevant exposures. *Food and Chemical Toxicology* 57:106-118.
2. Flari V, Boobis A, Hart A, Craig P, Rushton L. Structured expert knowledge elicitation on the differences in low-dose response relationship between different genotoxic carcinogens: feasibility study.

Research report

England, Northern Ireland and Wales

PDF

[View Interpretation of margins of exposure for genetic carcinogens- final report as PDF\(Open in a new window\)](#) (672.31 KB)

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PDF

[View Interpretation of margins of exposure for genotoxic carcinogens - Final report for objective 1 as PDF\(Open in a new window\)](#) (272.93 KB)

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[View Interpretation of the margin of exposure for genotoxic carcinogens as PDF\(Open in a new window\)](#) (2.09 MB)

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[View FSA project: t01051-Interpretation of margins of exposure for genotoxic carcinogens as PDF\(Open in a new window\)](#) (778.08 KB)

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[View FSA project T01051 Interpretation of Margins of Exposure for Genotoxic Carcinogens Final Report for Objective 02 as PDF\(Open in a new window\)](#) (247.27 KB)

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[View Interpretation of margins of exposure for genotoxic carcinogens - FSA project T01051 as PDF\(Open in a new window\)](#) (346.34 KB)

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[View Report of second expert workshop on differences in low-dose response relationship between various classes of genotoxic carcinogen as PDF\(Open in a new window\)](#) (628.74 KB)