



Frankfurt, 8 May 2007

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Dear Professor Farmer,

Following discussions between members of the Polyelectrolyte Producers Group (PPG) and Maureen Meldrum (HSE) and Jon Battershill, I am writing to request a review of the mutagenicity of acrylamide by the Committee on Mutagenicity. In particular, we request that the Committee assess whether the scientific data available support the existence of a threshold to the *in vivo* clastogenic response to acrylamide.

There are many difficult, scientific questions which should be addressed in this review. Acrylamide has an extensive and robust database and some of the key scientific issues relating to its genetic toxicology are briefly summarized below:

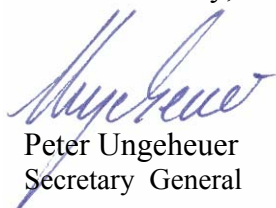
- Acrylamide is a weak somatic cell clastogen producing chromosome aberrations and micronuclei. It is negative in the Ames test, but its metabolite, glycidamide, is positive. Recently, strains of Salmonella have been developed which contain CYP2E1 and can metabolize acrylamide to glycidamide. However, under these conditions, acrylamide is not positive when tested in these strains.
- Acrylamide induces oxidative stress, and there is a relationship between development of oxidative stress and chromosome damage. In a comprehensive study evaluating the micronucleus response in mice, the threshold for the micronucleus response appears to correlate with the dose at which oxidative stress starts. Micronucleus induction is currently being analyzed against administered dose of acrylamide and glycidamide as measured by haemoglobin adducts and hepatic DNA adducts. At issue is whether the micronucleus response is logarithmic or linear with these dose markers. The response from this extensive study is also being evaluated for deviation from linearity by a quadratic model and also by applying statistical analysis for the presence of a threshold.

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- A paper recently accepted for publication has demonstrated the mode of action for the cytogenetic lesions. Acrylamide, at very low doses, inhibits several kinesin related proteins. These proteins are responsible for chromosome aggregation and movement during mitosis. Inhibition of this enzyme activity is a threshold phenomenon.
- Glycidamide reacts with DNA in the 7-position of guanine and to a much lesser extent the 7-position of adenine. Data are accumulating from other materials such as ethylene oxide that have shown that these reaction sites are not relevant to the induction of gene mutations.

We feel that the complexity of the data and the robustness of the database clearly warrant a Committee discussion at the soonest possible opportunity. Should the Committee be favourable to our request we will submit the results of the above cited study as well as all the other relevant data in the manner in which you would prefer.

Yours sincerely,

A handwritten signature in blue ink, appearing to read 'Peter Ungeheuer', is written over a light blue horizontal line.

Peter Ungeheuer
Secretary General

cc: Maureen.Meldrum@hse.gsi.gov.uk
Jon.Battershill@dh.gsi.gov.uk