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DNA adducts as biomarkers of exposure to some dietary carcinogens

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ABSTRACT

Humans are exposed to many chemicals via intake of food and drink and there are strong associations between dietary factors and cancer. Exposure to the dietary carcinogens acrylamide and acetaldehyde are potential health risks that have made the headlines. High levels of acrylamide are found in various food items, such as potato chips. Acetaldehyde exposure in association with alcoholic beverages is clearly linked to increased cancer risk. In addition, acetaldehyde is a contaminant and present or produced in various foods, including certain dairy products.

Dietary exposure is normally assessed from levels in food together with consumption patterns. However, with such assessments it is difficult to take into account the metabolic changes to the various chemicals, as the interindividual variations are great. Efforts have therefore been made to improve measurements of internal exposure by use of biomarkers, such as DNA adducts.

The aim of this thesis was to develop and apply biomarkers for human exposure to acrylamide and acetaldehyde. This was done by characterizing the DNA adduct N1-(2-carboxy-2-hydroxyethyl)deoxyadenosine (N1-GA-dA), formed by glycidamide) and the adducts N^2-ethyl-2'-deoxyguanosine (N^2-ethyl-dG) and N^6-ethyl-2'-deoxyadenosine (N^6-ethyl-dG), both formed by acetaldehyde. In addition, LC-MS/MS and ^{32}P-postlabeling methods for the analysis of these DNA adducts were developed and used to analyze animal and human DNA and tissue samples.

The glycidamide-derived DNA adduct N1-GA-dA was for the first time shown to be formed when mammalian cells were treated with glycidamide. However, the adduct was not detected in liver DNA of mice exposed to acrylamide.

The adduct N^2-ethyl-dG was detected in DNA treated in vitro with acetaldehyde, in human lung DNA from smokers and non-smokers and for the first time in DNA exposed in vitro to cannabis smoke. N^2-Ethyl-dG was also analyzed in leukocyte DNA from a group of healthy men who had consumed a moderate amount of alcohol under controlled circumstances. Adduct levels were not significantly increased. The chemical stability of N^2-ethyl-dG was studied and the findings imply that the rate of loss is more rapid than previously thought.

With the ^{32}P-postlabeling assay developed for the analysis of acetaldehyde adducts, it was shown for the first time that N^6-ethyl-dA is formed in DNA in vitro exposed to acetaldehyde.

Sensitive biomonitoring methods were developed and several novel findings were made. The methods used could be applied in future animal and human studies of exposure to glycidamide and acetaldehyde. In order to make these biomarkers useful for epidemiological studies, they must be fully validated and future biomarker studies should aim for analysis of multiple endpoints in a large number of samples.

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