Development of methods for the assessment of the health effects from mixtures of food additives

Area of research interest: Chemical hazards in food and feed
Study duration: 2006-06-01
Project code: T01040/41
Conducted by: TNO

Background

T01040 & T01041 aimed to develop methods to assess the health effects of mixtures of four food additives: butylated hydroxytoluene (E321), curcumin (E100), propyl gallate (E310) and thiabendazole (E233); known to individually produce liver effects in animal studies. These particular additives were chosen on the basis that the ILSI-Europe Acceptable Daily Intake Task Force had concluded combined actions or interactions might occur between them under experimental conditions. To assess whether there were any interactions the additives were tested individually and in various statistically determined combinations.
These projects were a continuation of previous work performed for our organisation's funded Project T01021.

The aim is to test the additives both individually and in various statistically determined combinations, to assess whether there are any interactions between the chemicals. This project is a continuation of previous work performed in the FSA-funded project T01021 and will be performed in collaboration with project T01041. T01040 will focus on study design, analysis of gene expression and statistical analysis of results. T01041 will focus on conducting studies in rat and human liver cells. BHT, CC, PG and TB are known to produce liver effects in animal studies.

Research Approach

An *in vivo* 28-day study has been performed in rats as part of T01021, with BHT, CC, PG and TB tested as individual components and in mixtures.

Gene expression analysis will be undertaken on liver samples from this study in order to assess whether gene expression changes induced by mixture exposures are similar to gene expression changes induced by individual additives.

Based on the results of the *in vivo* studies outlined above, dose levels and parameters will be selected to be employed in *in vitro* rat and human liver studies, for comparison of *in vitro* and *in vivo* results for the rat, and to provide information on potential differences in response between rats and humans.

A 28 day dietary administration study was performed in rats, with the four food additives tested individually, and as mixtures of pairs of additives and mixtures of all four additives. Gene expression analysis was undertaken on liver samples to assess whether changes in gene expression induced by mixture exposures were similar to gene expression changes induced by individual additives.

Results

No evidence of combination effects leading to overt liver toxicity were apparent, based on conventional toxicological endpoints. However, induction of Glutathione S-tranferase enzyme activity was observed, and the use of transcriptomics highlighted interactions at the genomic level.

Individually, of the four food additives studied, the most marked effects on liver metabolism were produced by butylated hydroxytoluene and thiabendazole. However, at the dose levels examined none of the four food additives appeared to be markedly hepatotoxic.

The binary and quaternary mixtures of the food additives had no major interactions with respect to liver and body weight in male Sprague-Dawley rats treated for 28 days. In most instances the toxic effect produced by a mixture of the additives was equivalent to that expected by simple summation of their individual effects. However, genomic interactions were observed with a 4 to 14-fold lower expression of CYP1A2 mRNA than expected; in addition glutathione S-transferase enzyme activity was shown to be induced. However, it should be noted that these mechanistic interactions do not cause a noticeable change in physiology, other than those which can already be predicted by simple addition effects caused by the individual additives. Therefore, from a hazard perspective, the study indicates that additional liver enlargement invoked by mixtures of these additives appears to be unlikely, even at high dose levels.

Research report

England, Northern Ireland and Wales

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