# DNA adductomics to unravel the causal link between red meat digestion and colorectal cancer

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Epidemiological research has demonstrated that the consumption of red and processed meat significantly contributes to colorectal cancer (CRC) risk, although the exact underlying cause has not yet been fully elucidated. At the time, the main red meat-CRC hypothesis is based on the fact that red, but not white meat consumption, has been linked to CRC, and that red meat like e.g. beef contains more heme iron than white meat like e.g. chicken. More specifically, said 'heme hypothesis' states that the ingestion and digestion of heme iron stimulates the formation of N-nitroso compounds (NOCs) and lipid peroxidation products (LPOs). Both NOCs and LPOs can induce DNA adduct formation, which is known to be the initiating factor of chemically induced carcinogenesis. Since the implementation of a top-down DNA adductomics approach can accommodate the assessment of environmental exposure to genotoxic chemicals, a novel DNA adductomics methodology was developed to enable in-depth investigation of diet-, and more specifically, NOC- and LPO-related DNA adduct formation. To this purpose, an in-house diet-related DNA adduct database, containing known alkylation as well as oxidation induced DNA adduct types, and a high resolution mass spectrometry (HRMS) based methodology were established [1]. After successful validation, the state-of-the-art UHPLC-HRMS DNA adductomics platform was implemented to investigate the genotoxic effects of red *vs*. white meat digestion. More specifically, beef (model for red meat) and chicken (model for white meat) were digested *in vitro* (static model) as well as *in vivo* (Sprague-Dawley rats), followed by DNA adductome mapping, univariate and multivariate (e.g. OPLS-DA) statistics. Combining the results from 3 independent *in vitro* and 1 *in vivo* digestion experiment(s), 7 DNA adduct types, including $O^6$-carboxymethylguanine, dimethyl- or ethylthymine, methylguanine, heptanalguanine, a malondialdehyde-guanine adduct, and a malondialdehyde-cytosine adduct could be singled out as potential red meat digestion markers [2]. This is highly relevant to the red meat-CRC hypothesis because the formation of the retrieved DNA adduct types may be linked to DNA alkylation and/or oxidation by e.g. NOCs and/or LPOs. Follow-up research should therefore focus on the role of DNA adduct formation in the red meat-CRC pathway, as well as the mutagenic potential and human *in vivo* relevance of the proposed DNA adduct markers.

**Keywords:** Colorectal cancer, DNA adductome mapping, Gastrointestinal digestion, Red meat

[1] Hemeryck L.Y. et al. (2015), *Analytica Chimica Acta*.
[2] Hemeryck L.Y. (2017), *UGent PhD Dissertation*.