# Peroxidized Fatty Acids in the Diet, Liver Inflammation, and Hepatocarcinogenesis

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Western style diet often contains high levels of peroxidized fatty acids, which may be cytotoxic and genotoxic. The impact of lipid peroxidation products on carcinogenesis in the liver and other organs is incompletely understood. We therefore studied the effects of peroxidized corn oil and its major peroxidized constituent, i.e. linoleic acid proxide (LOOH), on the unaltered cells and cancer prestages in the liver.

Corn oil (containing ~50% linoleic acid) was processed yielding a standardized content of lipid peroxides. This preparation was given to male rats as single gavage. Animals were sacrificed between 5 and 23 hrs post application. The degree of hepatic lipid peroxidation was determined by the TBARS-assay and by glutathione-related parameters. Livers were perfused with collagenase and the isolated cells were separated into hepatocytes, Kupffer and endothelial cells. Each of the cell types was incubated with LOOH for up to 24 hrs.

In vivo, rancid con oil led to a > 3-fold increase in liver TBARSs and a drop in hepatic GSH content indicating severe lipid peroxidation in the liver. When LOOH was applied in vitro, it was cytotoxic for all liver cell types. In Kupffer and endothelial cells LOOH induced a pronounced induction of heparin-binding epidermal growth factor-like growth factor (HB-EGF) mRNA. The elevation of the message could be abrogated by inhibiting p38MAPK, which may indicate that p38MAPK prolongs the stability of the HB-EGF mRNA. In a previous work we have found that HB-EGF is a very strong mitogen for initiated/preneoplastic hepatocytes in primary culture (S. Sagmeister et al, J Hepatol 2008). Thus, intake of LOOH via the diet may pose an increased risk to human health.

We conclude that enteral application of peroxidized fatty acids causes pronounced hepatic lipid peroxidation. The peroxidized linoleic acid induces synthesis of HB-EGF in the liver mesenchyme which may lead to outgrowth of liver preneoplasia.