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## ACCEPTED MANUSCRIPT

# Relative levels of dietary EPA and DHA impact gastric oxidation and essential fatty acid uptake

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#### Abstract

Previous research showed that increasing the proportion of DHA in marine lipid supplements significantly reduces associated health benefits compared with balanced EPA:DHA supplementation [1]. It was therefore hypothesized that the EPA and DHA molecules might have differential resistance to oxidation during gastric digestion, and the oxidation level achieved could be inversely correlated with intestinal absorption and, hence, with the resultant health benefits. Accordingly, we tested this proposed mechanism of action by investigating the degree of oxidation in the stomach, and the levels of bioaccessible lipids, of varying molar proportions of DHA and EPA (2:1, 1:1, and 1:2) using the dynamic gastrointestinal tract model TIM-1. In addition, small intestine enterocyte absorption and metabolism were simulated by Caco-2 cell monolayers that were incubated with these same varying proportions of DHA and EPA, and comparing oxidized and non-oxidized PUFA. The results show an inverse correlation between lipid oxidation products in the stomach and the levels of bioaccessible lipids. The balanced 1:1 EPA:DHA diet resulted in lower oxidation of PUFAs during stomach digestion relative to the other ratios tested. Finally, cell-based studies showed significantly lower assimilation of oxidized EPA and DHA substrates compared to non-oxidized PUFA, as well as significant differences between the net uptake of EPA and DHA. Overall, the present work suggests that the correct design of diets and/or supplements containing marine lipids can strongly influence the stability

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