



**Karolinska  
Institutet**

**Institutionen för biovetenskaper och näringslära**

# **The Paradox of Micronutrients**

**- *In vitro* and Human Studies**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorexamen vid Karolinska Institutet offentligen försvaras i Hörsalen, plan 4, Novum, Huddinge

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av

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## ABSTRACT

Many essential micronutrients found in fruits and vegetables exhibit antioxidant properties, protecting against oxidation and oxidative stress. Their ability to react with electrons also enables them to act as *pro*-oxidants, causing damage opposed to preventing it. While fruit and vegetables rich in micronutrients generally protect against oxidative damage and related diseases, supplementation studies with micronutrients have not been verified to have the same health beneficial effect. In fact, even harmful consequences have been seen. The reason for the ambiguous results is still not fully understood and this thesis investigates some of the factors believed to be involved. The focus is on the effect of micronutrients on DNA lesions, potential contributors to cancer development. The thesis takes you into chemical properties of micronutrients (paper I and II), it also explores their health effects in two human studies (paper III and IV).

When investigating *pro*-oxidant properties of thirteen micronutrients in this thesis, two of them stood out oxidising the DNA nucleoside deoxyguanosine in a dose-dependent manner – namely vitamin A and vitamin C. Compounds permitted in supplements as either ‘vitamin A’ (four compounds) or ‘vitamin C’ (five compounds) also differed in their potencies to act as *pro*-oxidants. The combination of vitamin C and copper particularly stood out, inducing oxidation to pure deoxyguanosine, but also to the DNA of cells in culture, a potential concern since both are commonly found in multivitamin supplements.

In an observational study, the impact of folate/folic acid status, intake or genes on DNA lesions (uracil misincorporation, oxidative DNA lesions, DNA breaks) in mononuclear cells of 36 infertile women was explored. Folate and related parameters were found not to correlate with DNA lesions in these women with adequate folate status. Our results add to the carefully accumulating evidence indicating that, even though folate status has been associated with DNA lesions, the effect seems to be more evident in subjects with folate deficiency. An increased interest has been drawn towards micronutrient supplements imitating the natural content of fruit, vegetables and berries, as for example with berry extracts. This thesis report on a cross-over intervention study where chronic kidney disease patients were administered a supplement containing oil extracts from the sea buckthorn berry rich in micronutrients and fatty acids. An eight-week administration did not affect their levels of DNA lesions (oxidative DNA lesions, DNA breaks) in minor salivary glands, nor mouth dryness or disease specific parameters.

Taken together, the results within this thesis add to the somewhat confusing evidence on micronutrient supplements and their properties and health effects. It emphasises that each micronutrient has unique properties, some with strong *pro*-oxidant activity dependent on factors in their immediate surrounding. The results also add to the growing evidence of a lack of effect on health from micronutrient supplements. It might be that supplementation with micronutrients provides best benefit in those with initially low nutrient levels.