Patients with chronic renal failure (CRF) suffer from a much higher cardiovascular morbidity and mortality. Cardiovascular diseases are the leading cause of death among these patients. The increased cardiovascular mortality in patients with CRF is due in part to the prevalence of established risk factors but also the uremic status per se seems to be accountable. Uremia leads to disturbances in water and electrolyte metabolism, changes in hormonal homeostasis, increased oxidative stress and accumulation of uremic toxins.

As one consequence these alterations lead to disturbances in nitroxide (NO) metabolism with development of a proinflammatory and prothombotic situation called endothelial dysfunction. This is the first step on the way to the morphological changes typical for atherosclerosis. In such a situation the activation of inducible nitroxide synthase (iNOS) in vascular smooth muscle cells (VSMC) could be a rescue mechanism providing enough NO for maintaining vascular homeostasis.

In the present study the effect of phenyl acetic acid (PAA) on the expression of iNOS in mononuclear leucocytes was investigated. PAA was characterized as a new uremic toxin that derive from phenylalanine metabolism and accumulate in the body of patients with end - stage renal disease.
Using TaqMan - RT - PCR phenyl acetic acid was shown to inhibit iNOS - mRNA - expression in mononuclear leucocytes from healthy subjects.in a dose - dependent manner- Since iNOS is expressed in both VSMCs and leukocytes the latter may be a suitable model to study iNOS expression and the effects of PAA on iNOS expression in leucocytes may therefore be extrapolated to VSMC.

The inhibiting influence of PAA on iNOS expression was found in concentrations that were also measured in plasma from patients with end - stage renal disease. Using western - blot analysis this effect is also detectable in the murine macrophage cell line RAW 264.7 on protein - level.

A decline in iNOS - activity has important pathophysiological relevance in end - stage renal disease and the effects of PAA described in this study may contribute to reduced NO - bioavailability in end - stage renal failure.
Insofar PAA meets the conditions that characterize an uremic toxin: it is found in the body of patients suffering from chronic renal failure in concentrations much higher than that found in healthy control subjects and it leads to a disturbance in NO metabolism.