A causative connection was suggested between the sharp increase in prevalence of inflammatory bowel diseases (IBD) and the consumption of processed foods. Carrageenan (CGN) (E407) is a common food additive, used as a thickener, stabilizer, and texturizer. Since the 1970s, CGN has been in public debate. Extensive in vitro and in vivo studies pointed out conflicting effects of CGN on intestinal health, reflected in a recent report from the WHO that disputed all claims against the use of CGN and in contrast a recent report from the EFSA that called for a re-evaluation of CGN safety. We used a physiologically digested food-grade CGN (pdCGN) in combination with different intestinal epithelial models, to elucidate impacts of pdCGN on gut health. We found that pdCGNs caused a disruption of an epithelial monolayer and immune-cell recruitment in a 3-D cellular co-culture system that mimics intestinal physiology. We also isolated a low molecular weight fraction from pdCGN that, when incubated with an epithelial monolayer, caused a time and dose dependent increase in Interleukin 8 expression, a cytokine associated with IBD. Moreover, pdCGN affected the inflammatory response of epithelial cells, in combination with iron or cytokines. In the iron co-stimulation model, pdCGN acted in synergy with iron and caused an increase in TNFα levels. In contrast, pdCGN combined with cytokines, decreased the inflammatory response up to abolishing its progression. Although the pathophysiology of intestinal pro-inflammatory effects induced by food-grade CGNs is not yet fully understood, we believe that our results contribute evidence to encourage further research on the safe use of CGN in food products.