

# Renal Epithelial Cell Vacuolisation Induced by Cumulative Doses of PEG, but Not PolyPEG®

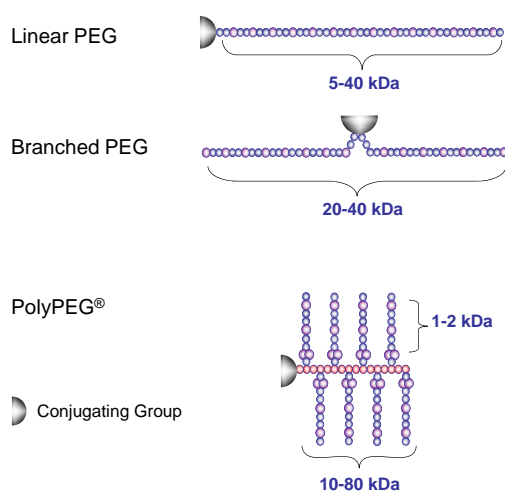
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## Introduction

Protein therapeutics are frequently modified by conjugation to polyethylene glycol (PEG) in order to overcome the serious limitations that can arise due to their short half-life, immunogenicity and/or toxicity<sup>1</sup> in the body. Several such PEGylated products have been approved. These rely on either multiple conjugations of relatively low molecular weight PEGs (ca. 5000), with consequent loss of biological activity, or conjugation of higher molecular weight PEGs (ca. 20-40kDa) that are not excretable or degradable. These approved PEGylated therapeutics are administered at low doses either infrequently or on a short-term basis such that the total cumulative dose of non-degradable PEGs is low.

With the advent of biologicals that require higher or more prolonged dosing, the issue of potential renal vacuolisation at relatively small dose multiples of the therapeutic dose, may become significant. PolyPEG® comprises a 'comb-like' arrangement of short PEG chains (typically 1-2 kDa molecular weight) attached to a polymethacrylate backbone by ester bonds<sup>2-5</sup>. PolyPEG® can therefore degrade via ester hydrolysis over time to yield low molecular weight units that are readily excreted. The amphiphilic nature of PolyPEG® may also improve biological activity, through a different interaction with protein surfaces.

**Fig. 1. Schematic representation of the structure of linear PEG, branched PEG and PolyPEG®**



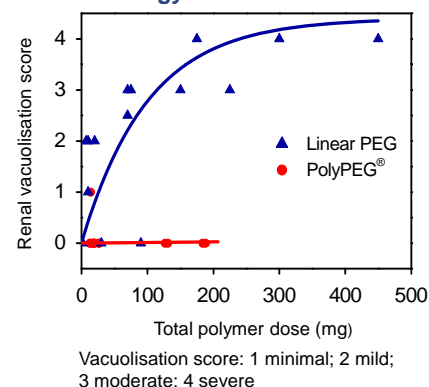
## Methods

Preclinical studies of pegylated proteins reported in the research and patent literature were analysed for total cumulative dose of PEG and renal vacuolisation score, determined histologically, and were collated. In addition, repeat dose studies of protein/PolyPEG® conjugates were also assessed in a similar manner.

## Results

The data from the meta-analysis indicate that linear PEG accumulates in vacuoles in renal epithelial cells on repeat dosing at relatively low cumulative doses, and that the severity of this is dose related<sup>6-8</sup> (Fig. 2). In contrast, PolyPEG® does not accumulate in vacuoles in renal epithelial cells in repeat-dose studies in mice (Fig. 2).

**Fig. 2. Meta-analysis of renal vacuolisation severity against cumulative dose in toxicology studies**



## Conclusions

These data indicate that PolyPEG® may have advantages as a half-life extension technology for those biologicals that will be dosed frequently over long periods, and/or at high doses.

### References

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