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Safety assessment of a novel ingredient for removable chewing gum

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ABSTRACT

Rev7™ is an indigestible gum polymer used for the manufacturing of chewing gum. It allows for the formulation of chewing gum with low adhesion; thus can be readily removed from surfaces such as sidewalks, clothing, carpets and furniture. In a toxicological safety assessment, Rev7™ was found to be non-mutagenic in the AMES assay. The highest concentration tested in a mouse lymphoma thymidine kinase locus gene mutation assay induced a slight but biologically relevant increase in mutations under non-metabolic activation conditions after 24 h. Because of this finding, a mouse micronucleus assay was performed, and the test article was found to be negative for inducing chromosomal damage. A 28-day repeated oral toxicity study resulted in a NOAEL of 80,000 ppm; the highest concentration tested. Rev7™ was found to be free from contaminants such as heavy metals, monomers, and solvents. Lastly, Rev7™ did not demonstrate skin-sensitizing properties in the murine local lymph node assay.

1. Introduction

The challenges of discarded chewing gum in the environment and the economic costs of cleaning up this litter have become serious issues; so much so that there are companies that now specialize in chewing gum removal (Milov et al., 1998; Strugatch, 2002). Rev7™ was specifically developed to aid in solving problems associated with discarded chewing gum, by being non-adhesive to surfaces often littered with gum.

Chewing gum is typically manufactured using an insoluble gum base blended with soluble sweeteners and flavorings. Chewing gum bases may be made of a single ingredient, or of a blend of ingredients, such as elastomers, resins, emulsifiers, waxes and fillers (Imfeld, 1999). The gum base typically comprises less than 50% of the final chewing gum product (Imfeld, 1999).

Gum bases typically utilize synthetic polymer elastomers to give them the necessary consistency and mastication properties desired for these products. While the elastomers used in gum bases have the necessary mechanical properties that make them ideal for chewing, these compounds are hydrophobic and highly adhesive to surfaces that contain hydrophobic components. Natural elastomers such as latex or vegetable sources such as chicle, which is composed of *cis*- and *trans*-polyisoprene (Rose and Steinbuchel, 2005) were predominantly used in the past. However, synthetic elastomers are more commonly used today in their place (Milov et al., 1998).

Rev7™ is a synthetic polymer that contains a maleic anhydride-grafted *cis*-polyisoprene backbone (Fig. 1). It additionally contains a hydrophilic component made of methoxypolyethylene glycol (MPEG), a commercially available polyethylene glycol with one of the two terminal hydroxyl groups capped by a methyl ether group. The addition of this hydrophilic component results in decreased adhesive properties to surfaces such as sidewalks, clothing, carpets, and furniture, and allows for the use of water to aid in the removal of the gum base from these surfaces.

To establish a safety profile for this novel synthetic polymer, Rev7™ was screened for a battery of compounds that could theoretically contaminate the product during the manufacturing pro-

Abbreviations: ADI, acceptable daily intake; BHT, butylated hydroxytoluene; DMSO, dimethyl sulfoxide; EC, European Community; EEC, European Economic Community; EU, European Union; FOB/MAct, functional observational battery/motor activity; GC, gas chromatography; GC/MS, gas chromatography–mass spectrometry; EO, ethylene oxide; GPC, gel permeation chromatography; GRAS, generally recognized as safe; GS/FID, gas chromatography with flame ionization detector; HPLC, high pressure liquid chromatography; ICP-MS, inductively coupled plasma-emission mass spectrometry; MTD, maximum tolerated dose; MPEG, methoxypolyethylene glycol; NOAEL, no observed adverse effect level; OECD, Organization for Economic Co-operation and Development; PEG, polyethylene glycol; Ph Eur, European Pharmacopeia; PIP, *cis*-polyisoprene; PIP-*g*-MA, polyisoprene graft maleic anhydride comb polymer; PS 580, polystyrene 580; PS 1010, polystyrene 1010; polystyrene 2450, polystyrene 2450; RDA, recommended daily allowance; RPMI/HS, Royal Park Memorial Institute Media with Human Serum; SCF, Scientific Committee on Food-European Commission; SI, stimulation index; THF, tetrahydrofuran; TK, thymidine kinase.

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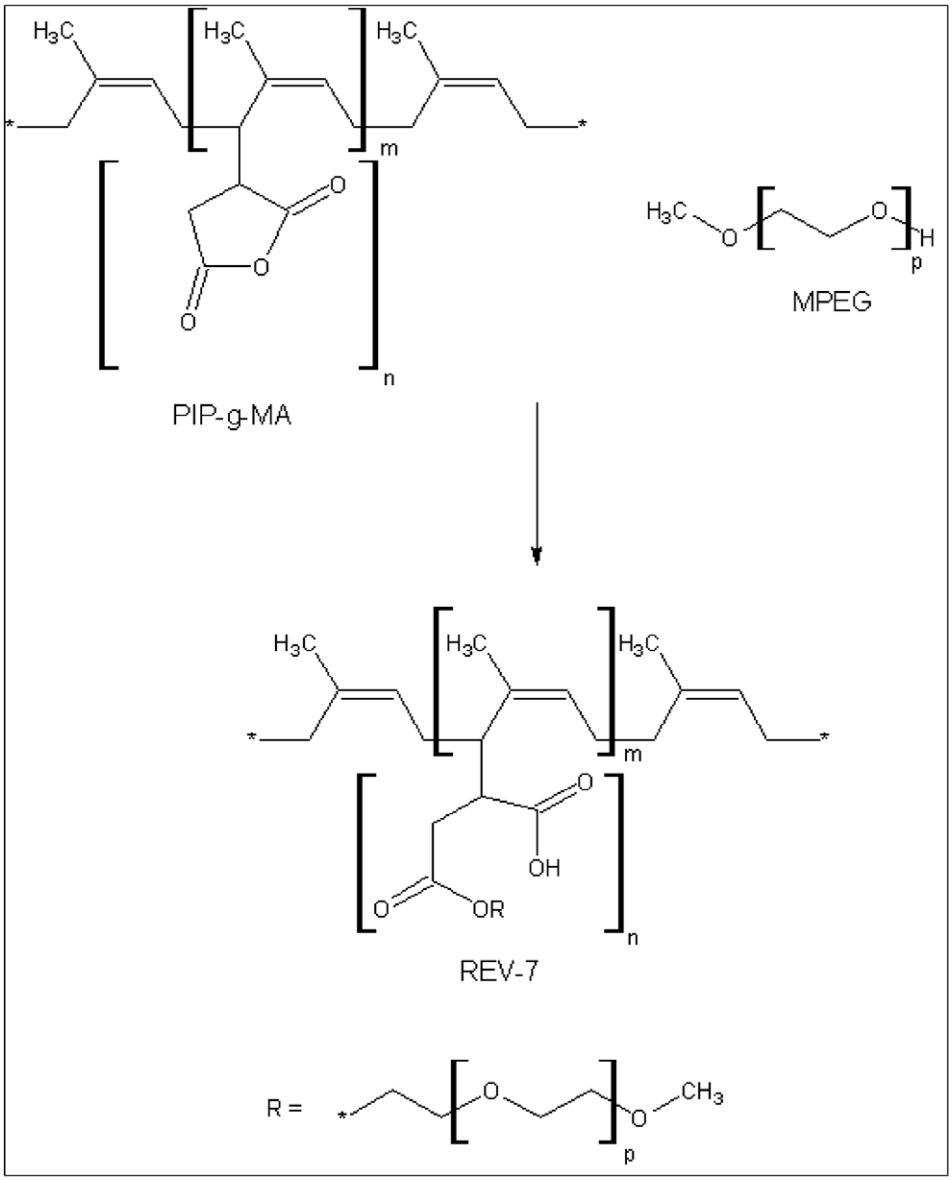

Fig. 1. A representation of the reaction between the components PIP-*g*-MA and MPEG to produce Rev-7™, where m = 366–1248, n = 3–15 and p = 44–50.

cess. These compounds include monomers, solvents, metals, and other potential by-products. In addition to this screening, several genetic and oral toxicology tests were performed, including the bacterial reverse mutation assay (AMES), the mouse lymphoma thymidine kinase gene mutation assay, the mammalian erythrocyte micronucleus test, and a 28-day repeated oral toxicity study in rats. Finally, in order to determine the possible risk of Rev7™ to cause skin sensitization reactions, a murine local lymph node assay was performed on the ingredient.

2. Materials and methods

2.1. Test article

The proprietary polymer and test article, Rev7™, is manufactured for Revolymer, Ltd. (Flintshire, United Kingdom). The backbone of Rev7™, referred to as PIP-*g*-MA, is made of *cis*-polyisoprene (PIP) with approximately three moles of maleic anhydride-grafted per polymer chain. PIP-*g*-MA is manufactured in a plant used to produce polymers for many applications. The manufacturer produces a contaminant-free product by ensuring only pure polyisoprene is produced immediately prior to PIP-*g*-MA, performing a hexane wash between grades, not supplying the first batch following changeover, and thorough testing of the final product to confirm that it meets specifications. Rev7™ is manufactured by reacting PIP-*g*-MA with methoxypolyethylene glycol (MPEG – pharmaceutical grade) using heat. The finished product is referred to as a comb polymer, because the MPEG chains hang from the PIP-*g*-MA backbone in a similar arrangement to the teeth found on a comb. The MPEG becomes chemically attached to the PIP-*g*-MA through the opening of the anhydride ring present on the PIP-*g*-MA molecule. The disappearance of the anhydride group is monitored using Fourier Transformation Infra Red (FT-IR). If necessary, excess anhydride is removed by water hydrolysis after the reaction is complete. The specification for anhydride concentration in Rev7™ is 15 μmol/g. The final product contains approximately 70% by weight of Rev7™, and 30% by weight of free and unbound methoxypolyethylene glycol (MPEG).

2.2. Chemical analyses of Rev7™

Chemical analyses were performed on Rev7™ to identify potential contaminants from raw materials, solvents, stabilizers, catalysts, neutralizing agents, or by-products from manufacturing. Screened compounds included heavy metals, monomeric and solvent residues, as well as butylated hydroxytoluene (BHT). These analyses were completed by specialized laboratories with expertise in the analysis of polymeric samples. All methods were validated by the addition of standards or use of a calibration curve where possible.