

SCIENTIFIC OPINION

Scientific Opinion on the safety of polyvinyl alcohol-polyethylene glycol-*graft-co-polymer* as a food additive¹

EFSA Panel on Food additives and Nutrient Sources added to Food (ANS)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to deliver a scientific opinion on the safety of polyvinyl alcohol-polyethylene glycol-*graft-co-polymer* (PVA-PEG *graft co-polymer*) as a film coating for food supplements. PVA-PEG *graft co-polymer* is a branched molecule consisting of about 75 % PVA and 25 % PEG units. The polymer is currently approved in pharmaceuticals in the EU. The specifications proposed are consistent with those for other already approved film-coating agents for use in the EU, including PVA and PEG, however, the Panel noted that no specifications for the impurities ethylene glycol, diethylene glycol, 1,4-dioxane and ethylene oxide are presently included. The co-polymer is not absorbed from the gastrointestinal tract. In repeated dose oral toxicity studies in animals (rat, rabbit, and dogs) no adverse effects were shown. No chronic toxicity/carcinogenicity studies were provided, but no adverse effects following long-term consumption of PVA-PEG *graft co-polymer* are expected given the absence of any substance-related adverse effects in the shorter-term toxicity studies and the fact that the co-polymer is virtually not absorbed following oral administration. Based on *in vitro* and *in vivo* assays the co-polymer is found to be not genotoxic. From a subchronic feeding study in the dog a NOAEL of approximately 800 mg/kg bw/day (highest dose tested) was identified. Conservative intake estimates from food supplements amounted to 4.3 mg/kg bw/day for children and 5 mg/kg bw/day for adults leading to a sufficient Margin of Safety compared to the NOAEL. From the maximum residual level of vinyl acetate Margins of Exposure of > 10⁶ were calculated. The Panel concluded that the use of PVA-PEG *graft co-polymer* food supplements as a film coating is of no safety concern at the proposed uses.

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KEY WORDS

polyvinyl alcohol-polyethylene glycol-*graft-co-polymer*; PVA-PEG *graft co-polymer*; CAS Registry Number 96734-39-3; coating food supplements; instant release film coating; PVA; PEG

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² Panel members: Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund, Pierre Galtier, David Gott, Ursula Gundert-Remy, Jürgen König, Claude Lambré, Jean-Charles Leblanc, Alicja Mortensen, Pasquale Mosesso, Agneta Oskarsson, Dominique Parent-Massin, Martin Rose, Ivan Stankovic, Paul Tobback, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen and Matthew Wright. Correspondence: ans@efsa.europa.eu

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to deliver a scientific opinion on the safety of the use of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer (PVA-PEG *graft* co-polymer) as an instant-release film coating for food supplements.

PVA-PEG *graft* co-polymer is a synthetic, branched, *graft* co-polymer consisting of approximately 75 % PVA and 25 % PEG units. The co-polymer is primarily intended for use in aqueous instant-release film coatings in the preparation and formulation of food supplement products.

The polymer is currently approved for use for pharmaceutical applications in various countries including the EU.

The Panel noted that, although the co-polymer is currently not approved as a food additive in the EU, the individual constituents of the polymer, PVA and PEG, are both approved for use as film-coating agents in the EU for food supplement products.

The specifications proposed for PVA-PEG *graft* co-polymer are consistent with those for other food additives already approved film-coating agents for use in the EU, including PVA and PEG. However, the Panel noted that no specifications for the impurities ethylene glycol, diethylene glycol, 1,4-dioxane, ethylene oxide and ethylene glycol are included in the proposed specifications for polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer by the applicant.

Following oral administration of a single dose of 1000 mg ¹⁴C-PVA-PEG *graft* co-polymer/kg bw to the rat, the compound was quantitatively excreted in the faeces within 168 hours. Excretion of the co-polymer in the urine, bile and via the in air exhaled carbon dioxide from the breakdown of ¹⁴C-PVA-PEG *graft* co-polymer, was negligible. The bioavailability of the co-polymer was calculated to be less than 1 %, indicating therefore virtually no absorption from the gastrointestinal tract. Overall, the Panel considered that absorption in humans is negligible.

The acute oral toxicity of PVA-PEG *graft* co-polymer in the rat was demonstrated to be low with the LD₅₀ >2000 mg/kg bw.

In repeated dose oral toxicity studies no treatment related effects were reported following administration of PVA-PEG *graft* co-polymer to laboratory animals (rats, rabbits, dogs).

In a 3-month study in the rat no adverse effects related to the oral administration of the co-polymer at dosed up to 15000 mg/kg in the drinking water. From this study the no-observed-adverse-effect levels (NOAELs) were determined to be about 1600 mg/kg bw/day for the male and 2200 mg/kg bw/day for the female rat, the highest dose tested.

In a 9-month dog study, an increase in the mean absolute ovary weight was reported in all the female treated groups at daily oral dose up to 811 mg PVA-PEG copolymer/kg bw/day, when compared to controls. The mean ovary weight of the control group was below the historical control range and the ovary weights of the treated groups were well within the historical control values. The Panel noted that in a 3-month study in the rat with oral doses up to 2200 mg/kg bw/day in females, no changes were recorded in the reproductive system even with histopathological examination. In addition no treatment-related findings in the combined fertility and pre- and postnatal toxicity test in rats were noted. Thus, the Panel concluded that the finding in the dog study was due to control and treated dogs being at different stage of the sexual cycle and their young age at the start of the study, and not directly related to the treatment. In agreement with the conclusion by the authors, the Panel considered the NOAEL to be about 800 mg/kg bw/day for both male and female dogs.

Negative results were obtained in *in vitro* and *in vivo* genotoxicity assays in both bacterial, as well as mammalian test systems indicating absence of any genotoxic effects.

No chronic toxicity/carcinogenicity studies were conducted with the co-polymer specifically, however no adverse effects following long-term consumption of PVA-PEG *graft* co-polymer are to be expected

based on the absence of any substance-related adverse effects in the shorter term trials and the fact that the co-polymer is, virtually, not absorbed following oral exposure.

In two prenatal developmental toxicity studies, no consistent, substance-related developmental effects were observed following oral administration of the co-polymer to female rats or rabbits at dose levels of up to 1000 mg/kg bw/day during gestation. All external, soft tissue, and skeletal observations in fetuses of the co-polymer-treated groups that were identified to be significantly increased in comparison to the concurrent controls, were spontaneous findings and/or occurred without a dose-response relationship. Furthermore, administration of PVA-PEG *graft* co-polymer had no adverse effects on the maternal animals with respect to parameters of general toxicity and gestation.

In a combined fertility and pre- and postnatal toxicity study conducted with Wistar rats, no adverse effects were attributed to the oral administration of PVA-PEG *graft* co-polymer to the F₀ males and females. Furthermore, F₁ pups and parental animals also demonstrated no adverse effects that could be related to the exposure to the co-polymer *in utero* and during the lactation period.

The overall NOAELs for parental F₀ and for pre- and postnatal developmental toxicity were determined to be 1000 mg PVA-PEG *graft* co-polymer/kg bw/day, the highest dose tested.

Data from the UK Food Standards Agency on the consumption of food supplements indicate that the use of food supplements among high consumers (97.5th percentile) ranged from 2 tablets/capsules per day in children (4-18 years old) to 7 tablets/capsules per day in adults. Based on the proposed coating level of 50 mg PVA-PEG *graft* co-polymer/tablet by the applicant, for high consumers an anticipated exposure of 100 mg PVA-PEG *graft* co-polymer/day for children and 350 mg PVA-PEG *graft* co-polymer/day for adults, corresponding to 4.3 mg/kg bw/day for children and to 5 mg/kg bw/day for adults, can be calculated. Assuming similar levels of use and intake data of PVA-PEG *graft* co-polymer from pharmaceuticals, the Panel calculated the combined intake from food supplements and pharmaceutical products to be respectively 8.6 mg/kg bw/day for children and 10 mg/kg bw/day for adults.

Considering that these estimates of intake were derived under the extremely conservative assumption that all food supplement products, as consumed on a daily basis, would be coated only with PVA-PEG *graft* co-polymer, these values are likely gross over-estimates of actual intakes of the co-polymer. Under these conservative assumptions, the consumption of PVA-PEG *graft* co-polymer from its use as a film-coating agent for food supplement products (i.e., 4.3 mg/kg bw/day for children and 5 mg/kg bw/day for adults) is approximately 190 to 160 times lower than the NOAEL of about 800 mg/kg bw/day (highest dose tested) derived from a 9-month feeding study in the dog.

Therefore, the Panel considered that the consumption of PVA-PEG *graft* co-polymer in film-coating formulations for food supplement tablets and/or capsules at the intended use level is not expected to present a risk to human health.

The Panel noted that vinyl acetate (VA) is a starting material used in the manufacturing process of PVA-PEG *graft* co-polymer and that the applicant proposed a residual level of unreacted VA of 20 mg/kg in the specifications. From the maximum residual levels of VA in PVA-PEG *graft* co-polymer (20 mg/kg), the Panel calculated for VA, Margins of Exposure (MOE) of 2.2×10^6 for adults and 2.5×10^6 for children. Therefore, the Panel considered that the presence of VA in PVA-PEG *graft* co-polymer up to 20 mg/kg would not be of safety concern.

The Panel concluded that given negligible absorption, the lack of genotoxic potential and the absence of effects at the highest doses tested in the subchronic and reproductive toxicity studies, there is no safety concern for the use of PVA-PEG *graft* co-polymer as a film coating at the proposed use levels.

TABLE OF CONTENTS

Abstract	1
Summary	2
Table of contents	4
Assessment	6
1. Introduction	6
2. Technical data.....	6
2.1. Identity of the substance	6
2.2. Specifications.....	6
2.2.1. Chemical specifications.....	6
2.2.2. Microbiological Specifications.....	7
2.2.3. Impurities.....	8
2.3. Manufacturing process.....	10
2.4. Methods of analysis in food.....	10
2.5. Reaction and fate in food.....	10
2.6. Case of need and proposed uses.....	11
2.6.1. Proposed levels of use	11
2.7. Information on existing authorisations and evaluations.....	11
2.8. Exposure assessment.....	13
3. Biological and toxicological data	14
3.1. Absorption, distribution, metabolism and excretion.....	14
3.2. Toxicological data.....	15
3.2.1. Acute oral toxicity	15
3.2.2. Short-term and subchronic toxicity	15
3.2.3. Genotoxicity	18
3.2.4. Chronic toxicity and carcinogenicity.....	19
3.2.5. Reproductive and developmental toxicity	19
4. Discussion.....	23
Conclusions	25
Documentation provided to EFSA	25
References	26
Glossary and abbreviations	29

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The use of food additives is regulated under the European Parliament and Council Regulation (EC) No 1333/2008 on Food additives⁴. Only food additives that will be included in the Community list in Annex II of that regulation may be placed on the market and used in foods under the conditions of use specified therein.

An application has been introduced for the authorisation of the use of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer as an instant-release film coating for food supplements. The coating protects food supplements against unpleasant tastes or odours, improves appearance and makes tablets easier to swallow.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The European Commission asks the European Food Safety Authority to provide a scientific opinion about the safety of the use of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer as coating agent on food supplements in accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002⁵.

⁴ Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, OJ L 354, 31.12.2008, p. 16.

⁵ Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L31, 1.2.2002, p. 1.

ASSESSMENT

1. Introduction

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to deliver a scientific opinion on the safety of the use of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer (PVA-PEG *graft* co-polymer) as an instant-release film coating for food supplements.

2. Technical data

2.1. Identity of the substance

The applicant stated that, consistent with the definition of a *graft* co-polymer, PVA-PEG *graft* co-polymer is a synthetic branched co-polymer with side chains [i.e., polyvinyl alcohol (PVA)] that are structurally different from the main polyethylene glycol (PEG) chain. PEG comprises the backbone of the polymer. Vinyl acetate (VA) is grafted onto the PEG backbone and the polyvinyl acetate side chains are subsequently hydrolyzed to form PVA side chains.

An average of 2 to 3 PVA side chains are grafted on to the starting material (i.e. PEG), which has a mean molecular weight of 6000 g/mol. The mean molecular weight of PVA-PEG *graft* co-polymer is 40 000 to 50 000 g/mol.

The chemical name is polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer. The substance has the CAS Registry Number 96734-39-3.

The polymer consists of approximately 75 % w/w PVA units and 25 % w/w PEG units. The co-polymer is primarily intended for use in aqueous instant-release film coatings in the preparation and formulation of food supplement products. The PVA-PEG co-polymer contains approximately 0.3 to 0.5 % colloidal silica to improve flow of the polymer powder.

The representative formula of the structural units of PVA-PEG co-polymer as provided by the applicant is shown in Figure 1.

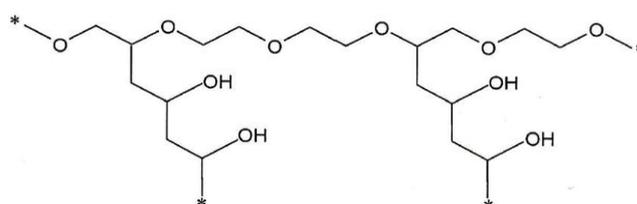


Figure 1: Representative formula of structural units of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer as provided by the applicant

Synonyms: macrogol poly(vinyl alcohol) grafted co-polymer; poly(ethan-1,2-diol-*graft*-ethanol); ethenol, polymer with oxirane, *graft* (CA Index name); oxirane, polymer with ethanol, *graft* (CA Index name); ethylene oxide-vinyl alcohol *graft* co-polymer.

2.2. Specifications

2.2.1. Chemical specifications

The applicant provided infrared (IR) and nuclear magnetic resonance (NMR) spectroscopic data characterising the substance.

Table 1: Chemical specifications for polyvinyl alcohol (PVA)-polyethylene glycol(PEG)-*graft*-co-polymer as proposed by the applicant.

Characteristic	Proposed specification
Definition	PVA-PEG <i>graft</i> co-polymer is a synthetic co-polymer that consists of approximately 75 % PVA units and 25 % PEG units; it may be combined with approximately 0.3 to 0.5 % colloidal silica ^a to improve its flow properties
Description	White to faintly yellow powder
Solubility	Freely soluble in water and dilute acids and dilute solutions of alkali hydroxides; practically insoluble in ethanol, acetic acid, acetone, and chloroform.
Purity	
IR Spectrum	Must comply
pH Value	5.0 to 8.0
Ester Value ^b	10 to 75 mg/g KOH
Dynamic viscosity	50 to 250 mPa·s
Loss on drying	Not more than 5 %
Sulphated Ash	Not more than 2 %
Heavy Metals	Not more than 20 mg/kg
Lead	Not more than 1 mg/kg
Vinyl Acetate	Not more than 20 mg/kg
Acetic acid/Total Acetate	Not more than 1.5 %

^aThe Panel assumed that the term ‘colloidal silica’ refers to the food additive E 551.

^bThe ester value is the number of mg of potassium hydroxide (KOH) required to saponify the esters in 1 g of sample

The Panel noted that no specifications for the impurities ethylene glycol, diethylene glycol, 1,4-dioxane and ethylene oxide, as listed in Table 3, are included in the proposed specifications for PVA-PEG-*graft*-co-polymer by the applicant.

As regards the term ‘heavy metals’ used by the applicant, the Panel noted that according to Commission Regulation (EU) No 231/2012⁶ the ‘*specifications should not make reference to the general parameter ‘heavy metals’ as this parameter does not relate with toxicity, but rather with a generic analytical method. Parameters related to individual heavy metals are toxicity related and are included in the specifications.*

The Panel further assumed that the terminology used by the applicant as regards ‘solubility’ complies with the terminology as proposed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2006) or the European Pharmacopoeia (Ph. Eur., 2011)⁷ being the solubility in water of 100-1000 g/L (temperature range 15 – 25 °C) and in ethanol < 0.1 g/L.

2.2.2. Microbiological Specifications

The applicant provided data on the microbial levels of three individual batches of the final product. The data are given in Table 2.

⁶ Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p.1.

⁷ European Pharmacopoeia, 2011. 7th edition

Table 2: Microbial analysis of production lots of polyvinyl alcohol(PVA)-polyethylene glycol(PEG)-*graft*-co-polymer

Specification Parameter	Specification limit (CFU/g)	Lot numbers		
		87194447G0	40692124U0	30220936W0
Total aerobic microbial count	Not more than 100	<100	<100	<100
Total combined yeast and moulds count	Not more than 10	<10	<10	<10

2.2.3. Impurities

The applicant indicated that the primary impurities identified in PVA-PEG *graft* co-polymer are carryover impurities from the starting materials, unreacted residues of the starting materials, residual solvents, reaction by-products, and heavy metals.

Impurities from starting materials

The applicant indicated that ethylene glycol, 1,4-dioxane, and ethylene oxide are known potential impurities of the starting material PEG. According to Commission Directive 2010/67/EU⁸, 1,4-dioxane and ethylene oxide are limited to levels of not more than 10 and 0.2 mg/kg in PEG, respectively. Ethylene glycol may occur individually or in combination with diethylene glycol at levels of not more than 0.25 % (w/w) or 2500 mg/kg.

The applicant provided analytical data on the levels of ethylene glycol, diethylene glycol, 1,4-dioxane, and ethylene oxide as a result of carry-over from the starting material in three individual batches of the final product. However, the applicant stated that, since ethylene glycol, 1,4-dioxane, and ethylene oxide are only impurities of the starting material, these have not been included in the specifications for PVA-PEG *graft* co-polymer. The data are given in Table 3.

Table 3: Chemical analysis of production lots of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer

Specification Parameter	ICH specification limit (mg/kg)	Lot numbers		
		87194447G0	40692124U0	30220936W0
Ethylene glycol	Not more than 620	<50	<50	<50
Diethylene glycol	Not more than 620	<50	<50	<50
1,4-Dioxane	Not more than 10	<10	<10	<10
Ethylene oxide	Not more than 0.2	<0.2	<0.2	<0.2

Unreacted starting materials

The Panel noted that VA is a starting material used in the manufacturing process of PVA-PEG *graft* co-polymer. The applicant proposed a residual level of unreacted VA of 20 mg/kg in the specifications. Furthermore, the Panel noted that according to the evaluation by the International

⁸ Commission Directive 2010/67/EU of 20 October 2010 amending Directive 2008/84/EC laying down specific purity criteria on food additives other than colours and sweeteners OJ L277, 21.10.2010, p. 17

Agency for Research on Cancer (IARC), VA is possibly carcinogenic to humans (Group 2B) (IARC, 1995). The Panel assessed the risk associated with the presence of VA (see discussion section).

Residual solvents

The applicant indicated that methanol residues occur in the final product at levels of less than 10 mg/kg.

The Panel noted that according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) guidelines for residual solvent impurities, methanol is a Class II solvent (i.e., solvents to be limited) and may occur in pharmaceuticals at levels of up to 3000 mg/kg.

According to Directive 2009/32/EC⁹, methanol may be used in the EU as an extraction solvent with residue levels in the final product not to exceed 10 mg/kg.

According to Commission Directive 2010/67/EU⁶, in PVA, a maximum level of 1 % (10000 mg/kg) has been set for methanol.

The applicant provided analytical data on the levels of methanol in three individual batches of the final product. The data are given in Table 4.

However, the applicant indicated that, since methanol could be replaced by a different other extraction solvent in the future, methanol has not been included in the specifications for PVA-PEG *graft* co-polymer.

Table 4: Levels of methanol in production lots of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer.

Specification Parameter	ICH Specification limit (mg/kg)	Lot numbers		
		87194447G0	40692124U0	30220936W0
Methanol	Not more than 3000	<10	<10	<10

Reaction by-products

The applicant indicated that acetic acid and methyl acetate are formed as by-products during the synthesis of PVA-PEG *graft* co-polymer. According to the proposed specifications (see Table 1) acetic acid (total acetate) may occur in the final product at levels of not more than 1.5 %.

PVA-PEG *graft* co-polymer was analyzed for levels of methyl acetate. Methyl acetate may occur in the final product at levels of less than 2 mg/kg.

According to Commission Directive 2010/67/EU⁸, methyl acetate has been limited to 1.0 % (10 000 mg/kg) in PVA.

The Panel noted that according to the ICH guidelines for residual solvent impurities, methyl acetate is a Class III solvent (i.e., solvents with low toxic potential), and methyl acetate levels of up to 5000 mg/kg would be considered acceptable without justification (ICH, 2011).

No limit for methyl acetate has been proposed in the specifications for PVA-PEG *graft* co-polymer. However, the applicant indicated that since methyl acetate is a potential reaction by-product, that it is

⁹ Directive 2009/32/EC of 23 April 2009 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients. OJ L144, 6.6.2009, p. 3

process-specific, and that it may be replaced by alternative solvents, no limit for methyl acetate has been proposed in the specifications for PVA-PEG *graft* co-polymer.

The applicant provided analytical data on the levels of methyl acetate in three individual batches of the final product. The data are given in Table 5.

Table 5: Levels of methyl acetate in production lots of polyvinyl alcohol(PVA)-polyethylene glycol(PEG)-*graft*-co-polymer

Specification Parameter	ICH specification limit (mg/kg)	Lot numbers		
		87194447G0	40692124U0	30220936W0
Methyl acetate	Not more than 5000	<2	<2	<2

2.3. Manufacturing process

The applicant provided detailed information on the manufacturing of PVA-PEG *graft* co-polymer. In summary, the substance is synthesized *via* a 2-step reaction process:

(1) a polymerization reaction, whereby PEG and VA are reacted together in the presence of a polymerization initiator (*tert*-butyl peroctoate in methanol) to form polyethylene glycol-*graft*-poly(vinyl acetate) co-polymer [PEG-*graft*-poly(vinyl acetate) co-polymer];

(2) a reaction whereby PEG-*graft*-poly(vinyl acetate) co-polymer is further reacted with sodium methoxide (MeONa) in methanol to form PEG-*graft*-poly(vinyl alcohol) co-polymer (PEG-*graft*-PVA co-polymer) and methyl acetate. No additional catalysts, other than *tert*-butyl peroctoate, are used.

The polymer solution is purified by steam distillation.

The applicant indicated that, in order to improve the flow properties of the polymer powder, colloidal silica at levels of approximately 0.3 to 0.5 % is introduced during a final spray drying processing step.

Silica is a food-grade anti-caking agent. The Panel assumed that the term ‘food-grade’ refers to the food additive, silica E551. In 1985; JECFA evaluated the safety of silica for use as an anti-caking agent and subsequently allocated an ADI “not specified” (JECFA, 1986).

2.4. Methods of analysis in food

No specific method of analysis in food is described by the applicant except that it is indicated that PVA-PEG *graft* co-polymer is identified using IR-spectrometry.

The applicant informed that PVA-PEG *graft* co-polymer is primarily intended for use as a film-coating agent on tablets and thus not added directly into the tablet core. The applicant stated that gravimetry (weight-difference between a coated and uncoated tablet) is used to assess the quantity of PVA-PEG *graft* co-polymer coated on the tablet. However the applicant did not indicate by which method the level of PVA-PEG *graft* co-polymer on a coated tablet is measured.

2.5. Reaction and fate in food

The stability of the co-polymer was evaluated under intermediate [30°C/70 % relative humidity (RH)] storage conditions for 36 months and accelerated (40°C/75 % RH) storage conditions for 6 months.

The applicant stated that the stability assays were conducted in accordance with the ICH guidelines for stability testing of new drug substances and products (ICH, 2003).

The stability data for 3 lots of PVA-PEG *graft* co-polymer provided by the applicant indicated that they were within the limits of the specifications for PVA-PEG *graft* co-polymer.

The applicant stated that since PVA-PEG *graft* co-polymer is readily soluble in water as well as acids and bases, it should not interfere with the release of the dietary supplement tablet ingredients.

The applicant further indicated that although no specific incompatibilities for the co-polymer with the active ingredients of the coated food supplements have been identified, a number of possible reactions have been described for both PEG and PVA. Since PEG and PVA possess terminal and secondary hydroxyl groups, respectively, these can be subject to esterification or etherification reactions (Rowe et al., 2009a,b).

Rowe et al. (2009a) also noted that liquid and solid PEG grades may be incompatible with some colouring agents, and that all PEG grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Rowe et al. (2009a) further indicated that migration of PEG can occur from tablet film coatings, leading to interaction with core components. However, according to the applicant, such reactions are not expected to occur for PVA-PEG *graft* co-polymer as the plasticizer is covalently bound in the co-polymer and cannot migrate into the tablet core. The Panel agreed with this view.

2.6. Case of need and proposed uses

According to the applicant PVA-PEG *graft* co-polymer is primarily intended for use in aqueous instant-release film coatings for food supplements to protect against unpleasant tastes or odours, improve appearance, make tablets easier to swallow, give a distinctive appearance and create a protective barrier.

2.6.1. Proposed levels of use

According to the applicant, PVA-PEG *graft* co-polymer-based film coating formulations are applied to food supplement tablets/capsules at 2 to 4 mg/cm². PVA-PEG *graft* co-polymer spray suspensions prepared in water can contain up to 20 % PVA-PEG *graft* co-polymer. On a dried basis, the co-polymer may comprise up to approximately 60 % of a pigmented coating formulation; however, for coating formulations without a pigment, PVA-PEG *graft* co-polymer may comprise 100 % of the dry coating.

A food supplement tablet would typically be coated such that the aqueous film coating formulation would provide a 5.0 % weight gain to the overall weight of the tablet/capsule. Depending on the particular coating formulation, PVA-PEG *graft* co-polymer is expected to comprise up to approximately 100 % of the weight of the formulation, and therefore may constitute up to 5.0 % of the weight of the tablet/capsule (*i.e.*, tablet capsule weight x 0.05 x 1.00).

2.7. Information on existing authorisations and evaluations

The applicant stated that PVA-PEG *graft* co-polymer has been used in the pharmaceutical industry as part of film coating agents for tablets and capsules for years. The co-polymer has been globally approved for use in the preparation of pharmaceutical products in a number of large global regions, including Europe, Japan, and the U.S.

A number of national pharmacopeias include monographs for the polymer. Specifically, official specifications for the pharmaceutical use of the co-polymer are provided in the *United States Pharmacopeia/National Formulary* (USP, 2011) and the *European Pharmacopoeia* (Ph. Eur., 2011).

PVA-PEG *graft* co-polymer has not been evaluated by JECFA. However, the individual constituents of the co-polymer (i.e. PVA and PEG) were evaluated by JECFA in 1979 (JECFA, 1980) and in 2003 (JECFA, 2004). Based on the available data the Committee allocated an ADI of 50 mg/kg bw/day for PVA and of 10 mg/kg bw/day for PEG.

EFSA evaluated PVA as a coating agent for food supplement tablets and/or capsules and concluded that the consumption of the PVA as specified in the opinion is not of safety concern (EFSA, 2005a).

EFSA also evaluated the use of PEG as a film coating agent for use in food supplement products and concluded that the use of PEG as specified in the opinion is not of safety concern (EFSA, 2006).

Additionally, PVA was evaluated by the IARC and assigned a Group 3 classification (i.e., the agent is not classifiable as to its carcinogenicity to humans) (IARC, 1987).

PVA-PEG *graft* co-polymer is currently not listed in the Codex General Standard for Food Additives (GSFA). The GSFA lists PVA for use in food supplements and PEG for use in five food categories (Codex Alimentarius, 2010a,b). PVA is permitted for use as a glazing agent and stabilizer. PEG is permitted for use as an adjuvant, antifoaming agent, carrier solvent, emulsifier, flavour enhancer, glazing agent, release agent, stabilizer, and thickener. Furthermore, the Inventory of Processing Aids lists PEG as a miscellaneous processing aid and an antifoam agent (Codex Alimentarius, 2008).

In the EU, PVA-PEG *graft* co-polymer has been registered in Germany since 2005 and in France, Britain, Spain, and Portugal since May 2007 *via* a mutual recognition procedure as a film coating agent in drug products. Both PVA (E 1203) and PEG (E 1521) are permitted food additives for use in the EU as coating agents for food supplement tablets and capsules (Annex II to Regulation (EC) No 1333/2008¹⁰).

In the UK specifically, PVA is permitted for use in non parenteral licensed medicines (Rowe et al., 2009b). In 1978, the Scientific Committee on Food (SCF) assigned a group tolerable daily intake (TDI) of 5 mg/kg body weight as a sum of PEG 300 to 4000 and triethylene glycol for use in the manufacture of regenerated cellulose films (SCF, 1978).

In the U.S., PVA is allowed for use as an indirect food additive in food contact materials and is approved for use as a diluent in colour additive mixtures for colouring shell eggs. For pharmaceutical use, PVA is used in drug products approved by the U.S. Food and Drug Administration (FDA) for use in several medical applications, including immediate release and sustained release tablet formulations (U.S. FDA, 2010).

PVA is included in the FDA Inactive Ingredient Database with a maximum amount of 20 mg per dosage unit for the oral route of administration (U.S. FDA, 2011). Additionally, PVA is affirmed as Generally Recognized as Safe (GRAS) for use in dietary supplements (U.S. FDA, 2004).

PEG (mean molecular weight of 200 to 9500) is permitted for use as a direct, multipurpose food additive (U.S. FDA, 2010), limited only by current good manufacturing practice (GMP). Additionally, PEG is a commonly used inactive ingredient in numerous pharmaceutical and dietary supplement products for oral administration and is included in the FDA Inactive Ingredient Database (U.S. FDA, 2011).

In Japan, PVA-PEG *graft* co-polymer is approved for use in pharmaceutical products. In August 2007, the co-polymer was granted approval as a new excipient for instant release coatings.

PVA and PEG are widely used in pharmaceutical and dietary supplement products in various countries in the Asia Pacific region. In Taiwan, PEG is approved for various food uses. Additionally, maximum permitted use levels of PVA and PEG for oral pharmaceutical products are specified in the Japanese Pharmaceutical Excipients Directory (JPED, 1996a,b).

¹⁰ Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12. 2008.

2.8. Exposure assessment

In 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been built from existing national information on food consumption at a detailed level. Competent authorities in the European countries provided EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA ‘Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment’ (EFSA, 2011)).

While the Panel normally uses the data on food consumption from the Comprehensive Database, in the case of PVA-PEG *graft* co-polymer and its proposed uses as a coating agent for food supplements, the Comprehensive Database does not provide reliable information because in most surveys the consumption data on food supplements has either not been reported or only for very few cases.

For previous opinions of the Panel on similar compounds (e.g. PVP/VA copolymer) (EFSA ANS Panel, 2010), the Panel used data from the UK Food Standards Agency on the consumption of food supplements which indicate that the use among high consumers (97.5th percentile) ranged from 2 tablets/capsules per day in children (4-18 year olds) (Gregory et al., 2000), to 7 tablets/capsules per day in adults (Henderson et al., 2002).

Based on these data, a tablet weight of 1000 mg and using a coating level of 50 mg PVA-PEG *graft* co-polymer per tablet (5 % on a 1000 mg tablet) for high consumers, the anticipated exposure estimate made by the Panel would be 100 mg PVA-PEG *graft* co-polymer/day for children, and 350 mg PVA-PEG *graft* co-polymer/day for adults, corresponding to 4.3 mg/kg bw/day for children (3-10 years, using 23.1 kg bw typical for children) and to 50 mg/kg bw/day for adults (using a default body weight of 70 kg).

The Panel assumed similar levels of use and intake of pharmaceutical products and food supplements per day (EFSA, 2005b). Given this assumption, the Panel estimated that the combined intake from food supplements and pharmaceutical products would be twice as high as the estimated intake for supplements only and would amount respectively for high consumers (97.5th percentile) to 8.6 mg/kg bw/day for children and to 100 mg/kg bw/day for adults.

The estimated exposure to PVA-PEG *graft* co-polymer based on these assumptions (coating level of 50 mg PVA-PEG *graft* co-polymer/tablet) are summarised in Table 6.

Table 6: Estimated potential exposure to PVA-PEG *graft* co-polymer from its use as food additive using proposed use levels of 5 % of tablet/capsule weight

	Estimated exposure to PVA-PEG <i>graft</i> co-polymer (mg/kg bw/day)			
	Estimated daily number of tablets	Food supplements	Pharmaceutical products	Total combined exposure
Children (3-10 years)	2	4.3	4.3	8.6
Adults	7	5	5	10

3. Biological and toxicological data

3.1. Absorption, distribution, metabolism and excretion

Leibold and Hoffman (2001) investigated the pharmacokinetic properties of the radioactively labelled co-polymer (^{14}C -PVA-PEG *graft* co-polymer) in Wistar rats (4/sex/group) following administration of single oral doses of 10 or 1000 mg/kg bw *via* gavage in a GLP-compliant study in accordance with EEC¹¹, OECD¹², and US EPA¹³ testing guidelines. The excretion of radioactivity in faeces, urine, and exhaled air was monitored for up to 168 hours post-dosing and in bile up to 48 hours post-dosing. Cumulative values for the excretion of radioactivity for each route (as percentages of the administered dose) are presented in Table 7.

Table 7: Mean cumulative excretion of radioactive material following administration of single oral doses of ^{14}C -PVA-PEG *graft* co-polymer to male and female rats

Dose (mg/kg bw)	Mean Cumulative Excretion of Radioactive Material (%) ^a							
	Faeces		Urine		Bile		Exhaled Air	
	Male	Female	Male	Female	Male	Female	Male	Female
	48 hours							
10	100.05	103.45	0.50	0.45	0.02	0.02	ND	ND
1000	100.76	105.27	0.27	0.22	0.01	0.01	ND	ND
	168 hours							
10	100.14	103.63	0.53	0.47	ND	ND	0.15	ND
1000	101.30	105.35	0.31	0.23	ND	ND	0.11	ND

^aAs percentage of administered dose; ND: not determined

Following a single oral dose of 10 mg/kg body weight of ^{14}C -PVA-PEG *graft* co-polymer, the cumulative amount of radioactivity recovered in the faeces at 168 hours post-dosing was approximately 100 and 104 % for male and female rats, respectively. In contrast, the total excretion of radioactivity via urine was negligible (i.e., 0.53 and 0.47 % for males and females, respectively). Excretion of $^{14}\text{CO}_2$ derived from ^{14}C -PVA-PEG *graft* co-polymer via exhaled air was also negligible at less than 1 % in both males and females.

Limited amounts of remaining radioactivity were detected in the carcass (i.e., 0.13 to 0.16 %), and the concentration of radioactivity was below 0.1 μg Eq/g or 0.1 mg/kg tissue in all organs and tissues. Mean total recoveries of radioactivity were determined to be approximately 101 and 104 % in male and female rats, respectively.

Similar results were obtained after a single oral dose of 1000 mg/kg body weight of ^{14}C -PVA-PEG *graft* co-polymer. At 168 hours post-dosing, the total amount of radioactivity excreted via faeces was approximately 101 and 105 % for male and female rats, respectively. Cumulative excretion of radioactivity via urine was 0.31 and 0.23 % for males and females, respectively. As at the lower dose level, excretion of $^{14}\text{CO}_2$ derived from ^{14}C -PVA-PEG *graft* co-polymer via exhaled air was negligible. Minimal amounts of remaining radioactivity were recovered in the carcass (i.e., 0.02 %) and the concentration of radioactivity was below 1 μg Eq/g or 1 mg/kg tissue in all organs and tissues. Mean total recoveries of radioactivity were determined to be approximately 102 and 106 % in male and female rats, respectively.

¹¹ EC Commission Directive 87/302/EEC of November 18, 1987; Part B: Methods for the determination of toxicity, Toxicokinetics; OJ L 133, p. 51-54, 1987.

¹² OECD Guidelines for Testing of Chemicals; Method No 417 Toxicokinetics, Version dated 4.4.1984.

¹³ U.S. EPA, Health Effects Guidelines, OPPTS 870.7485, Metabolism and Pharmacokinetics, August 1998.

In bile-duct cannulated rats, cumulative biliary excretion of ^{14}C -PVA-PEG *graft* co-polymer 48 hours post-dosing was 0.02 and 0.01 % of the administered radioactivity in the 10 and 1000 mg/kg body weight dose groups, respectively.

As there was virtually no absorption of ^{14}C -PVA-PEG *graft* co-polymer from the gastrointestinal tract following oral administration at 10 or 1000 mg, pharmacokinetic data of the co-polymer based on serum, plasma, or blood levels could not be determined.

Overall, the Panel considered, based on the excretion data, the absorption and oral bioavailability are negligible.

The applicant stated that, since there is no reason to expect a different absorptive profile for PVA-PEG *graft* co-polymer in humans in comparison to that observed in rats, studies to determine the pharmacokinetics in humans were determined to be not necessary given that in rats the co-polymer was not absorbed systemically to any significant degree. Consequently, in humans PVA-PEG *graft* co-polymer also is expected to pass unchanged through the gastrointestinal tract following oral consumption, with elimination of the unabsorbed material occurring largely *via* the faeces. The Panel considered that absorption in humans is negligible.

Leibold and Hoffman (2001) study has recently been published by Heuschmid et al. (2013a).

3.2. Toxicological data

3.2.1. Acute oral toxicity

Weimann and Hellwig (2000) tested the acute oral toxicity of PVA-PEG *graft* co-polymer in Wistar rats according to EEC, OECD, and US EPA/OPPTS testing guidelines. The study was carried out in compliance with GLP regulations. PVA-PEG *graft* co-polymer was administered as an aqueous suspension to young adult animals. Male and female fasted rats (3/sex) received a single oral dose of 2000 mg PVA-PEG *graft* co-polymer/kg bw, by gavage. The administration volume was 10 mL/kg bw. The animals were observed over 14 days for mortality and body weight gain.

Necropsy and gross pathological examinations were performed approximately 16 hours after withdrawal of the diet. No mortality and clinical signs of toxicity were observed. All animals gained body weight during the 14-day observation period. With the exception of 2 male rats with unspecified lung findings (i.e., diffuse reddish discoloration and oedema), no other abnormalities were noted at necropsy. In addition, there were no abnormalities in the gastrointestinal tract after the single administration of PVA-PEG *graft* co-polymer at 2000 mg/kg bw in any male or female rat.

The oral LD_{50} value after a single administration was determined to be greater than 2000 mg/kg bw for male and female Wistar rats.

3.2.2. Short-term and subchronic toxicity

Studies in rats

Mellert et al. (2001) evaluated PVA-PEG *graft* co-polymer in a 3-months- repeated dose study in Wistar rats (10/sex/group). The study was conducted according to EEC and OECD (408) guidelines and GLP. This study has recently been published by Heuschmid et al. (2013b).

Rats received PVA-PEG *graft* co-polymer at concentrations of 0 (vehicle control), 600, 3000, or 15 000 mg/kg in the drinking water (calculated by the authors to be equivalent to approximately 0, 58, 299, and 1611 mg/kg bw/day for males and 78, 365, and 2191 mg/kg bw/day for females).

Clinical signs and mortality were recorded daily. Food consumption, water consumption, and body weights were determined weekly. Ophthalmoscopy was performed before the start and at the end of

the study. Assessment of motor activity and clinical pathology, including haematology, clinical chemistry, and urinalyses were carried out towards the end of the administration period. At the end of the study all animals were killed and assessed by gross pathology, selected organs were weighed (liver, kidneys, adrenal glands, testes, epididymis, ovaries, uterus, thymus, spleen, brain and heart), and comprehensive histopathological examinations were conducted.

None of the animals died during the administration period. Several statistically significant changes in food consumption, water consumption (low- and mid-dose levels), body weight gain, and food efficiency were noted throughout the study; however, the authors considered these changes to be incidental due to their isolated occurrence and/or lack of a dose-response relationship. At the highest dose level of PVA-PEG *graft* co-polymer, water consumption was significantly increased in males (up to 31.4 %) and females (up to 37.2 %) compared to control animals. Although these effects were considered to be treatment-related by the authors, the origin and relevance of these findings were questioned as neither clinical chemistry nor histopathology revealed any associated substance-related findings.

Results from the detailed open field examinations and functional observational battery (FOB) including reflex tests, were comparable among all groups. Results of the motor activity assessment of treated and control animals also were comparable for all except one interval of the 12-interval trial (i.e., significant decrease in motor activity in mid- and high-dose males at interval 10). Given the isolated nature of this occurrence, these reductions were determined to be unrelated to treatment. Any ophthalmological observations were spontaneous in nature and equally distributed between treated and control animals. Clinical pathology examination revealed no variations in haematology, clinical chemistry, and urinalysis parameters in the treated groups compared to the control group.

At necropsy, mean absolute and relative organ weights were similar to those of controls. Only, a significant increase in mean absolute liver weights in low-dose males (58 mg/kg bw/day) and a significant decrease in mean relative brain weights in low- and high-dose males (58 and 1611 mg/kg bw/day) were observed compared to the male control group. The increase in mean absolute liver weight in the low-dose males was regarded as incidental due to the lack of any macroscopic or microscopic correlation in this dose group or in the other dose groups or sex. The authors attributed the significant decreases in the mean relative brain weights of the low- and high-dose males to the higher, not statistically significant, terminal body weights of these groups and considered these findings to be incidental occurrences.

There were no morphological alterations of the gastrointestinal tract in male or female rats following subchronic administration of PVA-PEG *graft* co-polymer at any of the dose levels. Gross lesions (i.e., erosion/ulceration of the glandular stomach, enlarged liver, and discolouration of the kidneys, missing testes, reduced epididymis, dilated uterus, and reduced thymus) occurred sporadically and were dispersed equally among all groups, including controls. No organ weight changes or organ or tissue alterations ascribable to the treatment were noted.

The no-observed-adverse-effect level (NOAEL) was considered by the authors to be 1611 mg/kg bw/day in males and 2191 mg/kg bw/day in females the highest doses tested. The Panel agreed with this conclusion.

Studies in dogs

Kaspers et al. (2002) evaluated PVA-PEG *graft* co-polymer in Beagle dogs (5/sex/group) in a 9-month study, performed according to GLP. This study has recently been published by Heuschmid et al. (2013b). PVA-PEG *graft* co-polymer was administered in the diet at concentrations of 0 (vehicle control), 3000, 10 000, or 30 000 mg/kg diet. The control and test drinking water solutions (400 mL) were added directly to the dogs' diet (400 g) and mixed into a paste. The mean intake of the co-polymer was calculated by the authors to be 77, 257, and 783 mg/kg bw/day for males and 82, 271, and 811 mg/kg bw/day for females. Clinical signs, mortality and food consumption were recorded

daily and body weights weekly. Clinical examinations were conducted prior to the start of the administration period and weekly thereafter. Ophthalmoscopy was performed before the start and towards the end of the administration period. Clinical pathology, including haematology, clinical chemistry, and urinalysis, were carried out prior to start of the administration period and thereafter at 3-month intervals. At the end of the experimental period (study days 275–281), the dogs were exsanguinated under anesthesia and necropsied. Organ weights (liver, kidneys, adrenal glands, testes, epididymis, ovaries, thyroid glands, spleen, brain, and heart) were recorded. Relative organ weights were calculated as percent body weight. Gross lesions and selected tissues from all animals underwent histopathological examination.

None of the animals died during the study period. Administration of PVA-PEG graft co-polymer had no influence on food consumption, body weight, or body weight gain. Single cases of transient diarrhea in a high-dose female on day 56 and transient soft faeces in 2 high-dose females between days 121 and 160 were assessed as incidental rather than substance-related. The detection of a palpable mass in the neck region of a mid-dose female from day 279 onwards was considered as not related to the administration of the compound.

Results from the detailed open field and ophthalmological examinations were comparable among all groups. The clinical pathology examination revealed a few significant changes in haematology (i.e., white blood cells, activated partial thromboplastin time), clinical chemistry (i.e., aspartate aminotransferase, magnesium), and urinalysis (i.e., squamous cells in sediment) parameters. As all of these changes were single occurrences with no dose-response relationship, they were determined by the authors to be not related to the treatment.

In low-dose (3000 mg/kg diet) males, a significant increase in absolute thyroid gland weight was observed compared to controls. The increase in absolute thyroid gland weights was regarded by the authors as incidental, given the absence of similar changes at the higher dose levels and in the opposite sex.

In all treated females groups, statistically significant increases were observed in the mean absolute ovary weights when compared to controls. The mean relative ovary weights were also increased compared to controls, but without statistical significance. As reported in Heuschmid et al. (2013b), the absolute weights of the ovaries of treated beagle dogs in this study (low-dose: 1450 mg; mid-dose: 1508 mg; high-dose: 1760 mg) were within the range of historical control of this laboratory (979–2258 mg; mean = 1378 mg from 169 control dogs in 31 studies) for dogs of the same strain and comparative age. The authors also reported that the ovary weights of the dogs in the control group of the study were unusually low (906 mg), even lower than the minimum value of historical control data. The histopathology of the reproductive organs of treated female and male dogs was unremarkable. Relative organ weights of all PVA-PEG *graft* co-polymer-treated groups were comparable to the control group. With the exception of glandular stomach mucosal erosions/ulcers in two high-dose (30 000 mg/kg diet) males and edema in the adipose tissue of mid-dose (10 000 mg/kg diet) females, the majority of gross lesions detected in the dogs were correlated with meaningful microscopic results, none of which were treatment-related as these microscopic findings were either single observations, observed in all or almost all groups at a comparable incidence and severity, or lacked a dose-response relationship. Although no further explanation for the 2 incidences of erosions/ulcers in the mucosa of the glandular stomach of the high-dose males was provided by the authors, given the isolated nature of this finding in only 2 of the 5 high-dose males and an absence of similar lesions in females, this is unlikely to be related to the administration of the co-polymer. In the absence of a dose-dependent response, the authors considered the oedema in the adipose tissue of a mid-dose female to have developed independently of PVA-PEG *graft* co-polymer treatment. There was no morphological evidence of any local intolerance in the gastrointestinal tract after subchronic administration of the co-polymer at any of the concentrations tested. Chronic lymphocytic thyroidadenitis (thyroiditis) was observed in 2 high-dose males. As dogs of the Beagle strain are known to be susceptible to chronic thyroidadenitis, these findings were considered by the authors not to be related to treatment. Based on these results,

histopathological examinations failed to demonstrate any substance-related organ lesion and no organ or tissue alterations indicating an adverse effect of PVA-PEG graft co-polymer were noted. According to the authors, the NOAEL was 783 mg/kg bw/day and 811 mg/kg bw/day in the male and female dogs, respectively.

3.2.3. Genotoxicity

In vitro studies

Engelhardt and Hoffmann (2000) tested PVA-PEG *graft* co-polymer in a reverse mutation assay conducted in accordance to EEC and OECD testing guidelines. The GLP-compliant standard plate test and pre-incubation test were conducted for 5 bacterial tester strains (*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and the tryptophan-requiring strain of *Escherichia coli* WP2 uvrA), each in the absence and presence of metabolic activation (S9 mix from the liver of Aroclor 1254-induced male Sprague-Dawley rats). The tester strains were exposed to PVA-PEG *graft* co-polymer (dissolved in water) at concentrations of 20, 100, 500, 2500, or 5000 µg/plate. Solvent (water) and several positive controls, including 2-aminoanthracene (2-AA), *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), 4-nitro-*o*-phenylenediamine (NOPD), 9-aminoacridine (AAC), and 4-nitro-quinoline-*N*-oxide (4-NQO), were used concurrently. The reference mutagen compounds were dissolved in DMSO. A slight decrease in the number of revertants and a slight reduction in bacterial growth were observed occasionally in various strains and test conditions from 2500 µg/plate onwards. Exposure to PVA-PEG *graft* co-polymer did not result in an increased number of revertant colonies with or without the S9 mix. The sensitivity of the test system used was demonstrated by the induction of an increased number of revertant colonies by the reference mutagens. Therefore, PVA-PEG *graft* co-polymer was determined to be neither a direct mutagen nor a pre-mutagen at the concentrations applied and under the experimental conditions chosen in the bacterial reverse mutation assay.

The potential of PVA-PEG *graft* co-polymer to induce gene mutations at the thymidine kinase (TK) locus was examined *in vitro* in mouse lymphoma cells (L5178Y/TK+/- cell line) in a microtitre assay (Engelhardt and Hildebrand, 2000). This GLP-compliant study was conducted in accordance with EEC and OECD testing guidelines.

Due to its known water solubility, the co-polymer was readily soluble in the aqueous culture medium [Roswell Park Memorial Institute (RPMI) 1640 medium]. A range-finding test demonstrated lack of cytotoxicity at concentrations of up to 5000 µg/mL.

Two independent experiments were carried out with and without metabolic activation (S9 mix from the liver of Aroclor 1254-induced male Sprague-Dawley rats). The first experiment was conducted using concentrations of 0, 313, 625, 1250, 2500, or 5000 µg/mL in the presence and absence of the S9 mix and the evaluation was done after an exposure time of 4 hours. For confirmation, a second experiment was performed using concentrations of 0, 78, 156, 313, 625, 1250, 2500, or 5000 µg/mL (without S9 mix; 24-hour exposure) and of 0, 313, 625, 1250, 2500, or 5000 µg/mL (with S9 mix, 4-hour exposure). RPMI 1640 medium supplemented with 5 or 10 % fetal calf serum (FCS) was used as the vehicle control during the 4- and 24-hour exposure periods, respectively, and methylmethanesulphonate (MMS) and cyclophosphamide (CPP) were used as positive controls concurrently. After a treatment period of 4 hours (with and without S9 mix) or 24 hours (without S9 mix), an expression phase of approximately 48 hours, and a selection period of approximately 10 days, the colonies of each test group were counted and the number of large and small colonies were determined. PVA-PEG *graft* co-polymer did not lead to an increase in the number of mutant colonies either with or without the S9 mix in 2 independently-performed experiments. The mutant frequencies at every concentration tested were within the ranges of the concurrent negative control values and historical control data. The sensitivity of the test system was confirmed as both positive control chemicals (i.e., MMS and CPP) led to the expected increases in the frequencies of forward mutations, while the vehicle controls resulted in mutant frequencies within the historically expected range for the L5178Y/TK+/- mouse lymphoma cell line. Thus, PVA-PEG *graft* co-polymer showed no mutagenic activity *in vitro* in the mouse lymphoma TK+/- forward mutation assay.

In vivo studies

Engelhardt and Hildebrand (2001) tested PVA-PEG *graft* co-polymer *in vivo* in the mouse bone marrow micronucleus assay. The GLP-compliant study was carried out according to EEC and OECD testing guidelines. Male NMRI mice (5/group) were administered intraperitoneally either 500, 1000, or 2000 mg/kg bw PVA-PEG *graft* co-polymer or purified water (vehicle control) twice at a 24-hour interval. The test substance was dissolved in purified water and applied at a volume of 10 mL/kg bw. Two groups were intraperitoneally administered single doses of 20 mg/kg bw of CPP or 0.15 mg/kg bw of vincristine sulphate (VCR) as positive controls. Following dosing, the animals were examined regularly, and any mortality or clinical signs reflective of potential reactions to the test compound were recorded. Bone marrow for micronucleus examination was prepared 24 hours after the last test substance or vehicle was administered. For positive control groups, bone marrow smears were prepared 24 hours after treatment. After staining of the preparations, 2000 polychromatic erythrocytes (PCEs) were evaluated per animal and investigated for micronuclei. The number of normochromatic erythrocytes (NCEs) with and without micronuclei occurring per 2000 PCEs also was determined. The ratio of PCEs to NCEs was determined to assess the inhibition of erythropoiesis. None of the animals died and no clinical signs of toxicity were noted in the animals treated either with the test substance, vehicle control, or the positive control substances (*i.e.*, CPP and VCR). Intraperitoneal administrations of PVA-PEG *graft* co-polymer did not lead to any increase in the number of PCEs containing either small or large micronuclei. The rate of micronuclei in all dose groups was within the ranges of the concurrent negative control and historical control data. Furthermore, no inhibition of erythropoiesis was detected. The sensitivity of the test system was confirmed as both positive control substances (*i.e.*, CPP for clastogenic effects and VCR for induction of spindle poison effects) led to the expected increases in the rate of PCEs containing small or large micronuclei. Based on these results, PVA-PEG *graft* co-polymer showed no chromosome-damaging (clastogenic) effect and there was no indication of an impairment of chromosome distribution in the course of mitosis up to the highest dose tested (2000 mg/kg body weight) as recommended by OECD.

The Panel noted that the route of administration is not relevant for human exposure. However, the Panel also noted that the compound would not be absorbed by the oral route and therefore no additional test was considered necessary.

3.2.4. Chronic toxicity and carcinogenicity

The applicant considered that, (i) taking into consideration the chemical structure of PVA-PEG *graft* co-polymer, (ii) no adverse effects were observed in 2 subchronic toxicity studies following repeat-dose administration of PVA-PEG *graft* co-polymer either in the drinking water of rats or in the food mixture of dogs (iii) taking into account the results of the genotoxicity testing and (iv) given the fact that PVA-PEG *graft* co-polymer is not absorbed to any significant degree and thus systemic exposure to the co-polymer following oral administration is negligible, it could be concluded that adverse effects related to longer term administration of PVA-PEG *graft* co-polymer also are not expected. Therefore, the Panel also considered that further evaluation of chronic toxicity and carcinogenicity was not necessary.

3.2.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity of PVA-PEG *graft* co-polymer was evaluated in prenatal developmental toxicity studies in rats and rabbits and in a combined fertility and pre- and postnatal developmental toxicity study in rats.

3.2.5.1. Prenatal developmental toxicity studies

Studies in rats

Gamer et al. (2002) examined PVA-PEG *graft* co-polymer for its potential impact on prenatal development when administered orally to rats during organogenesis. The study complied with GLP and ICH guideline on detection of reproductive toxicity of medicinal products.

Mated female Wistar rats (25/group) of the control, low-, mid-, and high-dose groups were administered 0 (bi-distilled water), 100, 300, and 1000 mg/kg bw/day of PVA-PEG *graft* co-polymer, respectively, at a dose volume of 10 mL/kg bw via gavage from days 6 to 15 (inclusive) of gestation. Animals were observed for clinical symptoms and food consumption and body weight were recorded at regular intervals. On day 20 of gestation, all surviving animals were killed by cervical dislocation and the fetuses were removed from the uterus. Fetuses were weighed, sexed, and examined for external abnormalities, soft tissue anomalies, and skeletal malformations.

None of the animals died during the study period. Compared to the control group, there were no changes in the dams treated with PVA-PEG *graft* co-polymer with respect to food consumption, body weight, body weight change, corrected body weight change (i.e., net maternal body weight change), and uterine weight. Clinical observations and necropsy findings were comparable among all groups. Twenty-one (21) to 25 dams per group had implantation sites at study termination. No toxicologically relevant differences between the control and the substance-treated groups in gestational parameters (i.e., conception rate, mean number of corpora lutea, total implantations, pre- and post-implantation losses, number of early and late resorptions, and number of live fetuses) were recorded.

PVA-PEG *graft* co-polymer treatment had no effect on the fetal sex ratio, placental weight, and fetal body weight.

The Panel agreed with the authors that the external, soft tissue and skeletal examinations of the fetuses revealed no toxicologically relevant differences between the control and the substance-treated groups.

PVA-PEG *graft* co-polymer induced no signs of maternal toxicity, had no influence on gestational parameters, and produced no signs of developmental toxicity in rats, therefore the Panel considered the NOAEL to be 1000 mg/kg bw/day, the highest dose level tested.

Studies in rabbits

Schneider et al. (2002) examined the potential prenatal developmental toxicity of PVA-PEG *graft* co-polymer following oral administration in Himalayan rabbits in a GLP-compliant study according to the ICH guideline on the detection of reproductive toxicity for medicinal products. Artificially inseminated female Himalayan rabbits (25/group) were administered the test substance at doses of 0 (bi-distilled water), 100, 300, and 1000 mg/kg bw/day (the highest recommended dose by gavage), respectively, at a dose volume of 10 mL/kg body weight via gavage from days 6 to 19 (inclusive) of gestation. Rabbits were observed for clinical symptoms and food consumption and body weight were recorded at regular intervals. On day 29 of gestation, all surviving dams were killed by intravenous injection of pentobarbital, and fetuses were removed from the uterus. Fetuses were weighed, sexed, and examined for external abnormalities, soft tissue anomalies, and skeletal malformations.

No significant differences in the number of mortalities were noted between the treated and control groups. Compared to controls, treatment with PVA-PEG *graft* co-polymer was not associated with any differences in the body weight, body weight change, corrected body weight change (i.e., net maternal body weight change), and uterine weight of dams in all dose groups. Differences in food consumption were observed between the substance treated groups and the control group, which was considered not to be treatment related. Clinical observations and necropsy findings, were comparable among all groups. 22 to 25 females per group had implantation sites at study termination. Examination of the gestational parameters revealed no significant differences between the control and the substance-treated groups in the conception rate, mean number of corpora lutea, total implantations, pre- and post-implantation losses, and number of resorptions. Although the mean percentages of live fetuses in all PVA-PEG *graft* co-polymer-treated groups were dose-dependently decreased, only the decrease in the high-dose group was statistically significant compared to the control group. This difference in the high-dose group was considered to be within the normal range of fluctuations for animals of this strain and age.

PVA-PEG *graft* co-polymer treatment had no effect on the fetal sex ratio, placental weight, and fetal body weight. No external malformations were observed in any of the PVA-PEG *graft* co-polymer-treated groups.

The Panel agreed with the authors that the external, soft tissue and skeletal examinations of the fetuses revealed no toxicologically relevant differences between the control and the substance-treated groups.

PVA-PEG *graft* co-polymer induced no signs of maternal toxicity, had no influence on gestational parameters, and produced no signs of developmental toxicity in rats, therefore the Panel considered the NOAEL to be 1000 mg/kg bw/day, the highest dose level tested.

Gamer et al. (2002) and Schneider et al. (2002) studies have recently been published by Heuschmid et al. (2013c).

3.2.5.2. Reproductive Toxicity Study

Schneider et al. (2003) investigated the potential of orally administered PVA-PEG *graft* co-polymer to affect the integrity and the performance of the male and female reproductive systems (i.e., gonadal function, oestrous cycle, mating behaviour, conception, gestation, parturition, lactation, and weaning), as well as the pre- and postnatal development of the progeny (i.e., neonatal morbidity, mortality, behaviour, growth, malformation, sexual maturation, learning, and memory). The GLP-compliant study was performed in accordance with the Commission Directive 91/507/EEC¹⁴ and the ICH harmonized tripartite guidelines Topic S5(R2) on detection of reproductive toxicity for medicinal products. Healthy young Wistar rats (25/sex/group) of the control, low-, mid-, and high-dose groups were administered 0 (bi-distilled water), 100, 300, and 1,000 mg/kg bw/day of PVA-PEG *graft* co-polymer, respectively, at a dose volume of 10 mL/kg bw via gavage. F₀ parental male rats were dosed at least 4 weeks prior to mating and during mating until 1 day before necropsy for a total period of approximately 6 weeks, while F₀ parental females were dosed 2 weeks prior to mating and during mating, gestation, and lactation until 1 day before necropsy for a total period of approximately 9 weeks. F₀ male and female animals from the same dose group were mated to produce a litter (F₁). Selected F₁ pups (25/sex/group) were reared to form the subsequent F₁ parental generation, but were not administered PVA-PEG *graft* co-polymer. Selected F₁ parental rats, whose F₀ parents were from the same dose group, were mated approximately 14 weeks after weaning to assess their reproductive capacity and the uterine content of the F₁ dams (i.e., F₂ implants). The non-selected F₁ pups were necropsied on day 21 after birth. The study was terminated by terminal necropsy of the F₁ parental females on gestation days 15 to 17.

All parental animals of both generations were examined regularly for mortality, clinical findings, food consumption, and body weight. Oestrous cycle length and normality were evaluated daily in F₀ and F₁ parental females for a minimum of 1 week prior to mating until insemination was confirmed. Mating and fertility indices were calculated for all parental females of both generations. In F₀ and F₁ parental males, various mating and fertility indices, as well as sperm parameters (i.e., motility, morphology, and sperm head counts) were investigated at scheduled necropsy. The delivered F₁ pups were sexed, weighed, and examined daily for mortality and clinical symptoms and at necropsy (day 21) for macroscopic abnormalities. Furthermore, all pups selected to form the F₁ parental generation were specifically monitored for parameters of sexual maturation (i.e., vaginal opening and preputial separation). Learning ability and memory also were assessed by a water maze test in preselected F₁ parental animals (12/sex/group) at an age of 34 to 36 days. At necropsy, all F₀ and F₁ parental rats and non-selected F₁ pups were examined by gross pathology with emphasis on the reproductive organs in the F₀ and F₁ parental rats. The weights of the ovaries, uterus, testes, seminal vesicles, prostate gland, total epididymides, and cauda epididymides were determined. Histopathological examinations were not conducted. Approximately 14 days after mating, the uterine content of the F₁ dams (i.e., F₂ implants) was examined.

¹⁴ Commission Directive 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. OJ L 270, 26.9.1991, 32–52.

Clinical examinations of all F₀ and F₁ parental animals revealed no indication of general toxicity in any of the groups. There were no significant differences in clinical findings or food consumption between the treated and control groups. The deaths of three F₀ males and one F₁ male were caused by gavage error and spontaneous chronic progressive nephropathy, respectively. There were several significant differences in the body weight changes of F₀ parental male and female test animals compared to controls. The majority of these changes were without a dose-response relationship, except for the increases in body weight changes observed in F₀ females on gestation days 18 to 19, where both changes in the mid- and high-dose groups reached statistical significance. Nevertheless, these changes were isolated occurrences and were considered to be of no toxicological relevance by the study authors. In F₁ mid- and high-dose parental males and females, significant decreases were observed in body weights compared to controls during the early post-weaning phase, but not later on in the study. However, these were determined to be a direct consequence of the fact that these animals were part of larger, although not statistically significant, litter sizes (i.e., greater number of F₁ pups per F₀ dam) that were observed at these dose levels. The larger litter sizes also were associated with significantly lower body weights of the high-dose F₁ pups (see below). Therefore, the decreased body weights observed in parental F₁ animals in the early post-weaning phase were a continuation of the significant body weight reductions observed in pups pre-weaning. The Panel agreed with this conclusion.

Gross pathological examinations, including organ weight determinations, of the F₀ females and F₁ male and female parental rats did not reveal any differences compared to the corresponding controls.

There were no adverse effects on fertility or reproductive parameters, based on oestrous cycle data, mating behaviour, and conception, gestation, and parturition rates in F₀ parental females. Although the total number of spermatids/g testis was significantly reduced in mid-dose males of the F₀ parental rats, the value remained within the historical range for controls. The significant increase in the relative weight of the testes of mid-dose F₀ males was regarded as a spontaneous finding.

In F₁ parental rats that were exposed to the co-polymer in utero from implantation until birth and via the milk from F₀ dams from birth until weaning, there were also no indications of adverse effects on fertility or reproductive parameters in either males or females. Overall, there was no indication of any pre- and postnatal developmental toxicity as all parameters recorded during gestation (i.e., conception rate, number of corpora lutea, number of implantations, and pre-implantation losses), lactation, and rearing were in the normal range of variations for animals of this strain and age. Notably, in F₁ dams of all PVA-PEG *graft* co-polymer-treated groups, significant decreases in post-implantation losses and total number of resorptions, as well as corresponding significant increases in the percentages of live fetuses, were observed; however, all values were within the historical ranges for controls. The majority of F₀ and F₁ parental rats were fertile. The scattered occurrences of several infertile rats among different groups, including the control groups, did not suggest any relation to treatment. Sperm analyses of these affected males and gross examinations of these affected male and female rats revealed no remarkable findings; thus, the observed number of pairs without progeny was considered to be spontaneous in nature.

At necropsy, the incidences of the macroscopic findings of the non-selected F₁ pups revealed several spontaneous findings were comparable between the treatment and control groups. Lastly, PVA-PEG *graft* co-polymer did not influence intrauterine development and survival of the F₂ implants.

Based on the results of this combined fertility and pre- and postnatal developmental toxicity study, the Panel considered the NOAELs for general toxicity in parental rats and for pre- and postnatal developmental toxicity to be 1000 mg/kg bw/day, the highest dose level tested.

Schneider et al. (2003) study has recently been published by Heuschmid et al. (2013d).

4. Discussion

The present application is for the use of PVA-PEG *graft* co-polymer as a film-coating agent in instant-release formulations for food supplement products.

PVA-PEG *graft* co-polymer is a synthetic, branched, *graft* co-polymer consisting of approximately 75 % PVA and 25 % PEG units. The co-polymer is primarily intended for use in aqueous instant-release film coatings in the preparation and formulation of food supplement products.

The polymer is currently approved for use for pharmaceutical applications in various countries including the EU.

The Panel noted that, although the co-polymer is currently not approved for use as a food additive in the EU, the individual constituents of the polymer, PVA (E 1203) and PEG (E 1521), are both authorised for use as film-coating agents in the EU for food supplement products.

The specifications proposed for PVA-PEG *graft* co-polymer are consistent with those for other, already approved, substances used as film-coating agents in the EU, including PVA and PEG. However, the Panel noted that no specifications for the impurities ethylene glycol, diethylene glycol, 1,4-dioxane, ethylene oxide and ethylene glycol are included in the proposed specifications for polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer by the applicant.

Following oral administration of a single dose of 1000 mg ¹⁴C-PVA-PEG *graft* co-polymer/kg bw to the rat, the compound was quantitatively excreted in the faeces within 168 hours. Excretion of the co-polymer in the urine, bile and via the in air exhaled carbon dioxide from the breakdown of ¹⁴C-PVA-PEG *graft* co-polymer, was negligible. The bioavailability of the co-polymer was calculated to be less than 1 %, indicating therefore virtually no absorption from the gastrointestinal tract. Overall, the Panel considered that absorption in humans is negligible.

The acute oral toxicity of PVA-PEG *graft* co-polymer in the rat was demonstrated to be low with the LD₅₀ >2000 mg/kg bw.

In repeated dose oral toxicity studies no treatment related effects were reported following administration of PVA-PEG *graft* co-polymer to laboratory animals (rats, rabbits, dogs).

In a 3-month study in the rat no adverse effects related to the oral administration of the co-polymer at dosed up to 15000 mg/kg in the drinking water were seen. From this study the NOAELs were determined to be about 1600 mg/kg bw/day for the male and 2200 mg/kg bw/day for the female rat, the highest doses tested.

In a 9-month dog study, an increase in the mean absolute ovary weight was reported in all the female treated groups when compared to controls. Based on the histopathology of the follicle and/or corpora lutea, the authors attributed this change to control and treated dogs being at different stages of the sexual cycle. The Panel noted that this could indicate an effect of the treatment on the sexual cycle of the animals. In an announced publication of these data (Heuschmid et al., 2013b), the authors concluded that the recorded differences in the oestrous cycle between control and treated female dogs could be related to using a randomization procedure based on body weights without consideration of sexual cycle status. It is also to be noted that in this study with small number of animals per group (5), with young animals (6-9 month of age at start of the study), and with a relative short duration (9 months), the chance of detecting a biologically significant effect on the oestrus cycle is very slim. In addition, the authors reported that the ovary weights of the dogs in the control group were unusually low (906 mg), below the lowest value of historical controls (979-2278 mg) for animals of the same strain and age. However, the Panel noted that the authors did not indicate if these historical control values reported in Heuschmid et al. (2013b), were collected from studies performed after or before the 2002 study. Finally the authors concluded that the observation of increased ovary weights in females from the treated groups was considered not related to the treatment.

The Panel noted that in a subchronic oral toxicity study in rats, no effects on weight and microscopic examination of reproductive organs were observed at dose levels up to about 1600 and 2200 mg/kg bw/day in male and female, respectively. In addition no treatment-related changes were observed in the combined fertility and pre- and postnatal toxicity test in rats in fertility, oestrus cycle, weight and microscopic examination of the reproductive organs, sperm parameters, sex ratio and sexual maturation of the F₁ pups and reproductive capacity of the F₁ generation up to the highest dose tested by gavage (1000 mg/kg bw/day). Consequently, the Panel considered that the effects reported in the 9-month dog study could be related to the specificities of the study such as the young age at the start of the study as well as the randomization procedure based on body weights without consideration of sexual cycle status, and therefore were not directly treatment related. This conclusion was further supported by the absence of such observation in the rats, which are known to be very sensitive to this kind of effect.

Negative results were obtained in *in vitro* and *in vivo* genotoxicity assays in both bacterial, as well as mammalian test systems indicating absence of any mutagenic or genotoxic effects.

No chronic toxicity/carcinogenicity studies were conducted with the co-polymer specifically, however no adverse effects following long-term consumption of PVA-PEG *graft* co-polymer are to be expected based on the absence of any substance-related adverse effects in the shorter term trials and the fact that, virtually, the co-polymer is not absorbed following oral exposure.

In two prenatal developmental toxicity studies, no consistent, substance-related developmental effects were observed following oral administration of the co-polymer to female rats or rabbits at dose-levels of up to 1000 mg/kg bw/day during gestation. All external, soft tissue, and skeletal observations in fetuses of the co-polymer-treated groups that were identified to be significantly increased in comparison to the concurrent controls, were spontaneous findings and/or occurred without a dose-response relationship. Furthermore, administration of PVA-PEG *graft* co-polymer had no adverse effects on the maternal animals with respect to parameters of general toxicity and gestation.

In a combined fertility and pre- and postnatal toxicity study conducted with Wistar rats, no adverse effects were attributed to the oral administration of PVA-PEG *graft* co-polymer to the F₀ males and females. Furthermore, F₁ pups and parental animals also demonstrated no adverse effects that could be related to the exposure to the co-polymer *in utero* and during the lactation period.

The overall NOAELs for parental F₀ and for pre- and postnatal developmental toxicity were determined to be 1000 mg/kg bw/day, the highest dose tested.

Data from the UK Food Standards Agency on the consumption of food supplements indicate that the use of food supplements among high consumers (97.5th percentile) ranged from 2 tablets/capsules per day in children (4-18 years old) to 7 tablets/capsules per day in adults. Based on a coating level of 50 mg PVA-PEG *graft* co-polymer/tablet for high consumers, an anticipated exposure of 100 mg PVA-PEG *graft* co-polymer/day for children and 350 mg PVA-PEG *graft* co-polymer/day for adults, corresponding to 4.3 mg/kg bw/day for children and to 5 mg/kg bw/day for adults can be calculated. Assuming similar levels of use and intake data of PVA-PEG *graft* co-polymer from pharmaceuticals, the Panel calculated the combined intake from food supplements and pharmaceutical products to be respectively 8.6 mg/kg bw/day for children and 10 mg/kg bw/day for adults.

Considering that these estimates of intake were derived under the extremely conservative assumption that all food supplement products, as consumed on a daily basis, would be coated only with PVA-PEG *graft* co-polymer, these values are likely gross over-estimates of actual intakes of the co-polymer. Under these conservative assumptions, the consumption of PVA-PEG *graft* co-polymer from its use as a film-coating agent for food supplement products (i.e., 4.3 mg/kg bw/day for children and 5 mg/kg bw/day for adults) is approximately 190 to 160 times lower than the NOAEL of about 800 mg/kg bw/day (highest dose tested) derived from a 9-month feeding study in the dog,

Therefore, the Panel considered that the consumption of PVA-PEG *graft* co-polymer in film-coating formulations for food supplement tablets and/or capsules at the intended use level is not expected to present a risk to human health.

The Panel noted that VA is a starting material used in the manufacturing process of PVA-PEG *graft* co-polymer and that the applicant proposed a residual level of unreacted VA of 20 mg/kg in the specifications. The Panel has derived previously (EFSA ANS Panel, 2010) a lower confidence limit on the benchmark dose (BMDL₁₀) of 440 mg VA/kg bw/day from the combined incidence of squamous cell carcinomas and papillomas in mice and rats induced by VA in the oral cavity as reported by Umeda et al. (2004). From the maximum residual levels of VA in PVA-PEG *graft* co-polymer of 20 mg/kg, the Panel calculated for VA, Margins of Exposure (MOE) of 2.2×10^6 for adults and 2.5×10^6 for children. Therefore, the Panel considered that the presence of VA in the PVA-PEG *graft* co-polymer, at a level up to 20 mg/kg would not be of safety concern.

CONCLUSIONS

The Panel concluded that given negligible absorption, the lack of genotoxic potential and the absence of effects at the highest doses tested in the subchronic and reproductive toxicity studies, there is no safety concern for the use of PVA-PEG *graft* co-polymer as a film coating at the proposed use levels.

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GLOSSARY AND ABBREVIATIONS

2-AA	2-aminoanthracene
AAC	9-aminoacridine
ADI	Acceptable Daily Intake
ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food
BMDL ₁₀	95% lower confidence limit of the benchmark dose for a 10% increase in tumor bearing animals
CAS	Chemical Abstracts Service
CGMP	Good manufacturing practice
CPP	Cyclophosphamide
DMSO	Dimethyl sulfoxide
EC	European Commission
EEC	European Economic Community
EU	European Union
EFSA	European Food Safety Authority
FCS	Fetal calf serum
FDA	Food and Drug Administration
FOB	Functional observational battery
GFSA	General Standard for Food Additives
GLP	Good Laboratory Practice
IARC	International Agency for Research on Cancer (IARC)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use
IR	Infrared
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JPED	Japanese Pharmaceutical Excipients Directory
LD ₅₀	Lethal Dose, 50 % i.e. dose that causes death among 50 % of treated animals
MMS	Methylmethanesulphonate
MNNG	<i>N</i> -methyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine
MPL	Maximum permitted level
NMR	Nuclear magnetic resonance
NCE	Normochromatic erythrocytes
NOAEL	No-observed-adverse-effect level

NOPD	4-nitro- <i>o</i> -phenylenediamine
4-NQO	4-nitro-quinoline- <i>N</i> -oxide
OECD	Organisation for Economic Co-operation and Development
PCEs	Polychromatic erythrocytes
PEG	Polyethylene glycol
PVA-PEG	Polyvinyl alcohol-polyethylene glycol- <i>graft</i> -co-polymer
PVA	Polyvinyl alcohol
RPMI	Park Memorial Institute
SCF	Scientific Committee on Food
TK	Thymidine kinase
USP	United States Pharmacopeia
VA	Vinyl acetate
VCR	Vincristine sulphate