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Re-evaluation of polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) as food additives and extension of use of polyvinylpyrrolidone (E 1201)

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Abstract

The present opinion deals with the re-evaluation of polyvinylpyrrolidone (E 1201, PVP) and polyvinylpolypyrrolidone (E 1202, PVPP) when used as food additives. One request for extension of use of PVP (E 1201) in foods for special medical purposes was also considered in this assessment. The Panel followed the conceptual framework under Commission Regulation (EU) No 257/2010 and considered that: the exposure assessment was based on the reported use and use levels (one food category out of the two food categories in which PVP and PVPP are authorised); the 95th percentile of exposure to PVP and PVPP of maximally 23.7 and 25 mg/kg body weight (bw) per day in children, respectively, was overestimated, because it was assumed that 100% of the food supplements consumed contained PVP or PVPP at the maximum reported use levels; the extension of use of PVP (E 1201) to foods for special medical purposes (FC 13.2) would result in an exposure of PVP of 4.3 mg/kg bw per day for children; the absorption of PVP and PVPP is very low; sufficient toxicity data were available for PVP; there is no concern with respect to the genotoxicity of PVP and PVPP; no carcinogenic effects were reported in carcinogenicity studies in rats at a dose of 2,500 mg PVP/kg bw per day, the highest dose tested; there is no need for chronic toxicity/carcinogenicity data for PVPP for the safety assessment of PVPP given the chemical similarity between PVP and PVPP, and the lack of adverse effects in the available repeated dose toxicity studies. Therefore, the Panel concluded that there is no need for numerical acceptable daily intakes (ADIs) for PVP and PVPP, and that there is no safety concern for the reported uses and use levels of PVP and PVPP as food additives. The Panel further concluded that the proposed extension of use is not expected to be of safety concern at the proposed maximum permitted level (MPL) and recommended consumption level.

Keywords: polyvinylpyrrolidone, E 1201, polyvinylpolypyrrolidone, E 1202, food additives, foods for special medical purposes

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Summary

The present opinion deals with the re-evaluation of polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) when used as food additives.

Polyvinylpyrrolidone (PVP, E 1201) and polyvinylypolypyrrolidone (PVPP, E 1202) are authorised as food additives in the European Union (EU) in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

Polyvinylpyrrolidone (E 1201) as a food additive was lately evaluated by JECFA in 1986 (JECFA, 1987). The previously adopted acceptable daily intake (ADI) of 0–25 mg/kg body weight (bw) was revised into 0–50 mg/kg bw, considering that the maximum limit for hydrazine in the final product was 1 mg/kg, and this level did not represent a significant risk. Polyvinylpolypyrrolidone (E 1202) as a food additive was evaluated by JECFA in 1983 and an ADI non-specified was proposed (JECFA, 1983). In the EU, polyvinylpyrrolidone (E 1201) as a food additive was evaluated by the Scientific Committee for Food (SCF) in 1990 (SCF, 1992). The SCF considered PVP as toxicologically acceptable for its use as an excipient in vitamins and sweeteners, on the basis of the summary data published by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1987 (that established an ADI of 0–50 mg/kg bw). SCF also concluded that 'If other uses in the future should significantly increase the potential intake the Committee would wish to review the original data'. Polyvinylpolypyrrolidone (E 1202) was evaluated by the SCF in 1990 (SCF, 1992). The SCF considered PVPP as toxicologically acceptable for the uses as a disintegration aid in tabletting and a processing aid in wine production, considering the expected limited exposure. SCF also concluded that 'If other uses should significantly increase the potential intake the Committee would wish to review the original data'.

One request for extension of use of PVP (E 1201) was also considered in this assessment. The request referred to an extension of use in foods for special medical purposes in tablet and coated tablet form (i.e. the food category 13.2 of part E of Annex II to Regulation (EC) No 1333/2008).

PVP and PVPP are homopolymers of the N-vinyl-2-pyrrolidone monomer. While PVP exhibits a linear polymeric structure, PVPP is cross-linked: the same CAS number (9003-39-8) is used to identify both polymers. E 1202 is produced by a polymerisation process that produces cross-linked insoluble polyvinylpyrrolidone. The infrared spectra of soluble polyvinylpyrrolidone (PVP) and insoluble polyvinylpyrrolidone (PVPP) do not reveal any differences. A main difference between both polymers is the solubility in water. According to information provided by the interested party, PVP polymers are identified based on the weight-average molecular weights derived from kinematic viscosity measurements (K-values). PVP grade K-25 or higher are compliant with the EU specification for E 1201 in respect to the minimum weight-average molecular weight required. Soluble PVP polymers are obtained by free-radical polymerisation of N-vinyl-2-pyrrolidone (NVP) in high purity water. Insoluble polyvinylpyrrolidone (PVPP) can be produced by the polymerisation of N-vinyl-2-pyrrolidone in the presence of either caustic catalyst or N, N'-divinyl-imidazolidone. According to the information provided by interested parties on particle size distribution of PVP and PVPP, the Panel could not exclude the presence of nanosized particles in the analysed materials.

Biological and toxicological studies have been provided by the interested party. No additional studies have been identified in the open literature. The Panel noted that the parameters and maximum limits established in the EU specifications for PVP and PVPP (except for lead and free N,N'-divinyl-imidazolidone) are included in the specifications for the pharmaceutical-grade products (European Pharmacopoeia, 2017). Therefore, the tested material(s) in toxicological studies complying with Pharmacopoeia meet also the EU specifications for E1201 and E1202.

The studies with radiolabelled PVP or PVPP in laboratory rats showed that the vast majority of the dose was found in the faeces with low amount in urine and bile and trace amounts of the radiolabel were detected in the organs. These observations indicated low absorption. The amount that was absorbed was mainly eliminated via the kidney.

Feeding of rats up to 9,000 mg PVP/kg bw per day in the basal diet for up to 90 days had no adverse effects. Feeding of dogs with PVP up to 2,500 mg/kg bw per day for 90 days showed no adverse effects. No treatment-related effects were seen in rabbits receiving up to 2,700 mg PVP/kg bw per day by gavage for 4 weeks.

PVPP had no adverse effects in rats receiving for 28 days a diet with containing up to 12,000 mg PVPP/kg bw per day or given by gavage a dose of 1,500 mg PVPP/kg per day for 90 days. Dietary administration of PVPP to rats for 90 days resulted in an no observed adverse effect level (NOAEL) of 9,000 mg/kg bw per day. In dogs, no treatment-related adverse effects were seen in 90-day studies in

which bolus doses of 1,000 mg PVPP/kg bw per day (capsules) or up to 4,800 mg PVP/kg bw (gavage) were administered for 6 months.

Based on the results of the available *in vitro* and *in vivo* studies on PVP and its precursor N-vinyl-2-pyrrolidone (NVP), and information on genotoxicity of the potential impurities 2-pyrrolidone (2-PY), N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone, N,N′-divinyl-imidazolidone and triethanolamine formate, the Panel concluded that PVP used as a food additive does not raise a concern with respect to genotoxicity. The Panel considered that this conclusion would also apply to PVPP. The Panel also noted that even under the scenario of 3% content of 2-PY in PVPP, the risk related to endogenous nitrosation of 2-PY is very low.

Chronic studies with 5,000 mg PVP (K-25 or K-30)/kg bw per day in rats or 2,500 mg PVP (K-30)/kg bw per day in dogs, both the highest dose tested, showed no toxicity or carcinogenicity. However, the Panel noted that these studies were limited in design and reporting. A well-conducted 2-year oral study in Sprague Dawley rats demonstrated that exposure to 2,500 mg PVP (K-90), the highest dose tested, is neither toxic nor carcinogenic. No chronic toxicity or carcinogenicity studies with PVPP were available.

No reproductive toxicity studies were available for PVP and PVPP; however, no effects on reproductive organs were observed in subchronic and chronic studies. No adverse developmental effects of PVP were observed in two prenatal developmental toxicity studies at the highest dose tested (5,000 mg/kg bw per day) after administration from gestation day (GD) 0–20. No adverse developmental effects were observed in the prenatal developmental toxicity study after administration of PVPP from GD 6–15 at the highest dose tested (3,000 mg/kg bw per day), and in a peri- and postnatal study after administration from GD 15 to postnatal day 21 at the highest dose tested (3,000 PVPP mg/kg bw per day).

Overall, the Panel considered that sufficient toxicity studies were available for PVP showing no adverse effects at the highest doses tested.

Based on the chemical similarity between PVP and PVPP, and the lack of adverse effects in the available repeated dose toxicity studies, the Panel considered that chronic toxicity data for PVPP are not necessary for the safety assessment of PVPP.

To assess the dietary exposure to PVP (E 1201) and PVPP (E 1202) from their use as food additives according to Annex II to Regulation (EC) No 1333/2008, the exposure to each of the additives was calculated based on the reported use levels. As both food additives are authorised in two food categories at QS and use levels were reported only for food supplements (FC 17.1), the food supplements consumers only scenario was used.

Mean exposure to PVP (E 1201) from its use as a food additive in food supplements ranged from 0.6 mg/kg bw per day in adults to 17.6 mg/kg bw per day in children. The 95th percentile of exposure to PVP (E 1201) ranged from 3.1 mg/kg bw per day in adolescents to 23.7 mg/kg bw per day in children.

For PVPP (E 1202), mean exposure ranged from 0.6 mg/kg bw per day in adults to 18.6 mg/kg bw per day in children. The 95th percentile of exposure to PVPP (E 1202) ranged from 3.3 mg/kg bw per day in adolescents to 25 mg/kg bw per day in children.

The Panel considered overall that the uncertainties identified resulted in an overestimation of the exposure to PVP (E 1201) and PVPP (E 1202) from their use as food additives according to Annex II in food supplements (FC 17.1). The Panel noted that food categories which may contain the additives due to carry-over (Annex III, Part 1, to Regulation (EC) No 1333/2008) were not considered in the current exposure assessment. This could result in an underestimation of the exposure. Data from the Mintel Database indicate that PVP or PVPP are not used in table-top sweeteners; therefore, leaving this food category 11.4.3 out of the exposure assessment is not anticipated to result in a major underestimation of exposure. The presence of PVPP in must, wine and wine products, and beers due to its use as a processing aid is assumed to be negligible owing to the employed filtration step during the production processes of these beverages.

Exposure to PVP (E 1201) resulting from the proposed extension of use of in foods for special medical purposes in tablet and coated tablet form (FC 13.2) was estimated based on an average daily consumption of two tablets, as recommended by the applicants, and a PVP level of 50 mg/tablet. The exposure for consumers of foods for special medical purposes (FC 13.2) would be therefore 100 mg per day, i.e. for adults, 1.4 mg/kg bw per day, for adolescents, 1.9 mg/kg bw per day and for children, 4.3 mg/kg bw per day.

According to the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA ANS Panel, 2014), the Panel considered that there is no need to allocate numerical ADIs for PVP (E 1201) and PVPP (E 1202).

According to the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA ANS Panel, 2014) and given that:

- the exposure assessment carried out by the Panel was based on the reported use and use levels (one food category out of the two food categories in which PVP and PVPP are authorised);
- the 95th percentile of exposure to PVP and PVPP of maximally 23.7 and 25 mg/kg bw per day in children, respectively, was overestimated, because it was assumed that 100% of the food supplements consumed contained PVP or PVPP at the maximum reported use levels;
- extension of use of PVP (E 1201) to foods for special medical purposes (FC 13.2) would result in an exposure of PVP of 4.3 mg/kg bw per day for children;
- the absorption of PVP and PVPP is very low;
- sufficient toxicity data were available for PVP;
- there is no concern with respect to the genotoxicity of PVP and PVPP;
- no carcinogenic effects were reported in carcinogenicity studies in rats at a dose of 2,500 mg PVP/kg bw per day, the highest dose tested;
- there is no need for chronic toxicity/carcinogenicity data for PVPP for the safety assessment of PVPP given the chemical similarity between PVP and PVPP, and the lack of adverse effects in the available repeated dose toxicity studies;

the Panel concluded that there is no need for numerical ADIs for PVP and PVPP, and that there is no safety concern for the reported uses and use levels of PVP and PVPP as food additives. The Panel further concluded that the proposed extension of use is not expected to be of safety concern at the proposed MPL and recommended consumption level.

The Panel recommend that the European Commission considers:

- revising of the EU specifications for PVP (E 1201) and PVPP (1202) in order to include better definitions and assays in line with the definitions;
- lowering the current limits for lead in the EU specifications for PVP (E 1201) and PVPP (E 1202) in order to ensure that both food additives will not be a significant source of exposure to lead in food.
- including in the EU specifications for PVP and PVPP, limits for several elements of toxicological importance analysed by the interested parties such as arsenic, cadmium, mercury, chromium, cobalt, copper and nickel;
- change the name of E1202 to 'crosslinked polyvinylpyrrolidone' (synonyms: Crospovidone, Crospovidonum, insoluble polyvinylpyrrolidone, cross-linked PVP, PVPP);
- replacing the term 'molecular weight (average)' by the term 'weight-average molecular weight' for PVP (E 1201) in the EU specifications;
- including a limit for 2-pyrrolidone in the EU specifications for PVP (E1201) and PVPP (E1202);
- revising the range for nitrogen content for PVP and PVPP in the EU specifications;
- including limits for the peroxide content, formic acid and triethanolamine formate in the EU specifications for PVP (E 1201), and for peroxide content in the EU specifications for PVPP (E 1202);
- requesting appropriate data on the potential presence of nanoparticles in PVP (E 1201) and PVPP (1202). The data should be generated in accordance with the EFSA Guidance (2018) and following the principle outlined in the latest Guidance (add the link of the latest one for PC), prior to consideration on the need for inclusion of particle size distribution as an additional parameter in the EU specifications.

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1. Introduction

The present opinion deals with the re-evaluation of polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) when used as food additives.

1.1. Background and Terms of Reference as provided by the European Commission

1.1.1. Background

Regulation (EC) No 1333/2008[1] of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010[2]. This Regulation also foresees that food additives are re-evaluated whenever necessary in the light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU[3] of 2001. The report "Food additives in Europe 2000[4]" submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

1.1.2. Terms of Reference

The Commission asks the European Food Safety Authority to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

1.2. Information on existing authorisations and evaluations

Polyvinylpyrrolidone (PVP, E 1201) and polyvinylypolypyrrolidone (PVPP, E 1202) are authorised as food additives in the EU in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

Polyvinylpyrrolidone (E 1201) as a food additive was lately evaluated by JECFA in 1986 (JECFA, 1987). In 1987, the concerns previously expressed were resolved regarding contamination with low levels of hydrazine. The previously adopted ADI of 0–25 mg/kg body weight (bw) was revised to 0–50

[1] 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. 16–33.
[2] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.
[3] COM(2001) 542 final.
[4] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002, 560.

mg/kg bw, considering that the maximum limit for hydrazine in the food additive was 1 mg/kg, and that this level did not represent a significant risk to health.

Polyvinylpolypyrrolidone (E 1202) as a food additive was evaluated by JECFA in 1983 and an ADI non-specified was proposed (JECFA, 1983).

In the EU, polyvinylpyrrolidone (E 1201) as a food additive was evaluated by the Scientific Committee for Food (SCF) in 1990 (SCF, 1992). The Committee was provided with information on metabolism, absorption, reticuloendothelial system (RES) accumulation, acute toxicity, short-term studies in rat, cat and dog, long-term feeding studies in rat and dog, teratogenicity studies, *in vitro* mutagenicity studies, a study of the effects on the canine immune system, data on the current levels of the contaminant hydrazine and observations in man. The SCF considered PVP as acceptable from a toxicological point of view for its use as an excipient in vitamins and sweeteners, on the basis of the summary data published by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1987 (that established an ADI of 0–50 mg/kg bw). The SCF also concluded that 'If other uses in the future should significantly increase the potential intake the Committee would wish to review the original data'.

Polyvinylpolypyrrolidone (E 1202) was evaluated by the SCF in 1990 (SCF, 1992). The Committee was provided with information on metabolism, short-term studies in rats and dogs and teratogenicity studies in rats, on the basis of which JECFA established an ADI non-specified in 1983. The SCF considered PVPP as toxicologically acceptable for use as a disintegration aid in tabletting and as a processing aid in wine production, considering the expected limited exposure. SCF also concluded that 'If other uses should significantly increase the potential intake the Committee would wish to review the original data'.

In 2002, the SCF evaluated the safety of the monomer (N-vinyl-2-pyrrolidone, NVP) residues in both food additives PVP and PVPP. The Committee considered that 'there was an adequate margin between worst case estimates of exposure to NVP from food, consumer goods and pharmaceutical preparations, and occupational exposures which have been shown not to be associated with serious human health effects. The Committee concluded that the intakes of NVP from food additive uses of PVP and PVPP did not give cause for concern'. The use of PVP in dietary supplements and of PVPP as a processing aid for beer and wine remained acceptable, provided that the existing specifications of PVP and PVPP were amended to set the proposed limit for NVP residues of 10 mg/kg PVP or PVPP. The Committee noted that the manufacturer supplying the EU market currently met such a specification. In the light of this conclusion, the SCF re-evaluated NVP as a food contact material (when used as a co-monomer in the production of thickening agents in adhesives for food packaging purposes) in 2002. On the basis of adequate migration data, the SCF classified it as SCF_list: 4A, only to be used in adhesives for paper and board and QMA < 10 μg/6 dm^2.

In 2006, the EFSA AFC Panel endorsed the previous SCF opinions and considering that the exposure to NVP from the use of PVP in food contact materials is in a similar range to the exposure from its use as excipient in food supplements, concluded that 'PVP is acceptable for use in food contact materials provided that the specifications for the food additive are met' (EFSA, 2006).

In 2010, the EFSA ANS Panel evaluated the safety of the co-polymer polyvinylpyrrolidone/vinyl acetate (PVP/VA) when used as a food additive. The ANS Panel considered the calculated Margins of Safety (MoS) for PVP/VA co-polymer sufficient and concluded that the residual level of hydrazine, proposed up to a maximum of 1.0 mg/kg in the final product, was unlikely to be of safety concern. Furthermore, the Panel concluded that the use of PVP/VA co-polymer in solid food supplements as a binding/coating agent was unlikely to be of safety concern at the proposed uses and use levels. However, the Panel considered that the level of hydrazine should be kept as low as reasonably achievable (EFSA ANS Panel, 2010).

Polyvinylpyrrolidone (E 1201) and Polyvinylpolypyrrolidone (E 1202) have also been reviewed by the Nordic Council of Ministers (TemaNord, 2002), who concluded that there was no need for a re-evaluation and that specifications should reflect the opinion of SCF of 2002, that residual monomer NVP should not exceed 10 mg/kg additive.

Polyvinylpyrrolidone is authorised in Pharmacopoeia Europea to be used in Medical Products, where it is known as Povidone. The European Medicines Agency (EMA) evaluated polyvinylpyrrolidone when used in medicinal preparations in 2014 (EMA, 2014).[5] The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the recommendation to suspend the marketing authorisation of methadone solutions via oral administration containing high molecular

[5] Available on: https://www.ema.europa.eu/en/medicines/human/referrals/methadone-medicinal-products-oral-use-containing-povidone.

weight povidone (known as K90). These compounds were suspended until they were reformulated. Additionally, the CMDh agreed that methadone tablets that contained low molecular weight povidone (e.g. K25 and K30) should remain on the market.

Polyvinylpyrrolidone is included in the Union list of authorised substances that may be intentionally used in the manufacture of plastic layers in plastic materials and articles (Annex I to Commission Regulation (EU) No 10/2011[6]). Furthermore, PVP is permitted as an antistatic/binding/emulsion for stabilising/film forming/hair fixing in cosmetic products (European Commission database – CosIng[7]).

Polyvinylpolypyrrolidone and polyvinylimidazole-polyvinylpyrrolidone copolymers (PVI/PVP) are also authorised to be used as clarifying and stabilising agents (e.g. in wine making) according to Regulation No 934/2019.

2. Data and methodologies

2.1. Data

The Panel on Food Additives and Flavourings (FAF) was not provided with a newly submitted dossier. EFSA launched public calls for data[8,9] to collect information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to the date of the last WG meeting.[10] Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based however these were not always available to the Panel.

One request for extension of use was also considered in this assessment. The request referred to an extension of use in foods for special medical purposes in tablet and coated tablet form (i.e. the food category 13.2 of part E of Annex II to Regulation (EC) No 1333/2008).

Food consumption data used to estimate the dietary exposure to polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) were derived from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database[11]).

The Mintel's Global New Products Database (GNPD) was used to verify the uses of polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) in food and beverage products and food supplements within the EU's market. The Mintel's GNPD is an online database that contains the compulsory ingredient information present on the label of numerous products.

2.2. Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee.

The FAF Panel assessed the safety of polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the Scientific Committee on Food (SCF, 2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

When in animal studies, the test substance was administered in the feed or in drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake is calculated by the Panel using the relevant default values. In case of rodents, the values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012) are applied. In the case of other animal species, the default values by JECFA (2000) are used. In these cases, the dose was expressed as 'equivalent to mg/kg bw per day'. If a concentration in feed or drinking water was reported and the dose in mg/kg bw per day was calculated (by the authors of the study report or by the Panel) based on these reported concentrations

[6] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1–89.
[7] Available online: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple
[8] Call for technical and toxicological data on miscellaneous food additives to be re-evaluated under the Regulation (EU) No 257/2010. Published: 11 August 2017. Available online: https://www.efsa.europa.eu/en/consultations/call/170811
[9] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 6). Available online: https://www.efsa.europa.eu/en/data/call/170223
[10] 7–8/11/2019.
[11] Available online: http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

and on reported consumption data for feed or drinking water, the dose was expressed as 'equal to mg/kg bw per day'.

Dietary exposure to polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) from their use as food additives was estimated by combining food consumption data available within the EFSA Comprehensive European Food Consumption Database with reported use levels submitted to EFSA following a call for data. One scenario was used to calculate the exposure (see Section 3.4). Uncertainties on the exposure assessment were identified and discussed.

In the context of this re-evaluation, the Panel followed the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EC) No 257/2010 (EFSA ANS Panel, 2014).

3. Assessment

3.1. Technical data

3.1.1. Identity of the substance

Polyvinylpyrrolidone (E 1201)

According to Commission Regulation (EU) No 231/2012, polyvinylpyrrolidone (E 1201) has chemical formula $(C_6H_9NO)_n$ and average molecular weight not lower than 25,000 g/mol; no EINECS (EC) or CAS identifiers are reported. The anhydrous substance must have a nitrogen content between 11.5 % and 12.8 %; polyvinylpyrrolidone is described as a white or nearly white powder, soluble in water and in ethanol but not in ether, and a pH in the range 3.0–7.0 for a 5% aqueous solution.

The Panel noted that the terminology used in the EU specifications for average molecular weight should correspond to weight-average molecular weight.

According to JECFA (2006a), PVP is identified with CAS No 9003-39-8.

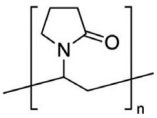

Figure 1: Structural formula of polyvinylpyrrolidone (re-drawn from JECFA (2006a))

According to information provided by the interested party (Documentation provided to EFSA n. 1, 2019), the actual PVP products available are identified with a parameter for viscosity (K-values, K-value ranges), and weight-average molecular weights reported in Table 1. The C- and K-type products with the same dimension value are the same product manufactured by the same process. According to the information from interested party, the C-type is used for pharmaceutical applications and is tested to ensure a low level of endotoxins and recommended when PVP free of pyrogens is required. As reported by the interested party, as the (average) molecular weight of PVP polymers increase, so do in general their solution viscosities, their glass transition temperatures and their adhesive properties. Historically, the determination of the polymer molecular weight was difficult and the K-value, derived from kinematic viscosity measurements of a PVP aqueous solution, was adopted to estimate molecular weights.

Table 1: K-value ranges and weight-average molecular weights for different PVP grades classified with the K-value (Documentation provided to EFSA n. 1, 2019)

Grade[(a)]	K-value range	Weight-average molecular weight (g/mol)
K-12 and C-12	10.2–13.8	4,000
K-17 and C-17	16.0–17.5	10,000
K-25	24–26	34,000
K-29/32 and C-30	29–32	58,000
K-90	85–95	1,300,000

(a): According to Ashland Specialities (2013),[11] a PVP product characterised by K-120 (108–130) was also marketed.

The Panel noted that, based on the above data, only PVP grade K-25 or higher is compliant with the EU specification for E 1201 with respect to the minimum average molecular weight.

According to the interested party[12] (Documentation provided to EFSA n. 2), 'PVP polymers are readily soluble in cold water, the concentration being limited only by viscosity: it is possible to prepare free-flowing solutions of PVP K-30 polymer in concentrations up to 60% with only moderate effect on density. PVP K-60 and K-90 polymers are available commercially as 45% and 20% aqueous solutions, respectively'. PVP K-30 polymer is freely soluble in many organic solvents, including alcohols and some chlorinated solvents such as chloroform, methylene chloride and ethylene dichloride.

Polyvinylpolypyrrolidone (E 1202)

According to Commission Regulation (EU) No 231/2012, polyvinylpolypyrrolidone (E 1202) is defined as 'a poly-[1-(2-oxo-1-pyrrolidinyl)-ethylene], cross-linked in a random fashion. It is produced by the polymerisation of N-vinyl-2-pyrrolidone in the presence of either caustic catalyst or N,N'-divinyl-imidazolidone'. The chemical formula given is $(C_6H_9NO)_n$. The anhydrous substance must have a nitrogen content between 11 % and 12.8%.

PVPP (E 1202) is produced by a polymerisation process that produces cross-linked insoluble polyvinylpyrrolidone. The infrared spectra of soluble polyvinylpyrrolidone (PVP) and insoluble polyvinylpyrrolidone (PVPP) do not reveal any differences (Documentation provided to EFSA n. 3, 6; Haaf, 1985; Bühler, 2008). For this reason, the interested party (Documentation provided to EFSA n. 2) considered that the chemical formula $(C_6H_9NO)_n$ assigned in the EU specifications shows the ratio of elements in the food additive E 1202.

The interested party (Documentation provided to EFSA n. 6) has clarified that the name polyvinylpolypyrrolidone and abbreviation PVPP are chemically inaccurate designations for E 1202, although they have been widely used and accepted in the area of food additives. A more accurate name for E 1202 would be 'crosslinked polyvinylpyrrolidone' (synonyms: Crospovidone, Crospovidonum, insoluble polyvinylpyrrolidone, cross-linked PVP, PVPP) and suggested also the following definition 'Crosslinked homopolymer of N-vinyl-2-pyrrolidone produced catalytically. It is insoluble in water and other common solvents'. The Panel agreed that the name 'polyvinylpolypyrrolidone' in the EU specifications are chemically inaccurate designations for E 1202.

The interested party (Documentation provided to EFSA n. 6) has also stated that they use the CAS no 9003-39-8 for both polyvinylpyrrolidone (E 1201) and cross-linked polyvinylpyrrolidone (E 1202).

For PVPP, the molecular weight or the K-value cannot be used as a means of identifying the different polymer types or grades since the substance is insoluble in water as well as in all the usual solvents and the measurement cannot be carried out (Bühler, 2008). According to information provided by the interested party, the solubility of PVPP is very low (< 1%) in acid, alcohol or water and the pH is not expected to have an influence on its solubility (Documentation provided to EFSA n. 6).

The Panel noted that, from the definition of the assay in the EU specifications, the percentage content of nitrogen in both polymers is within a similar range, with solubility in water being a main difference between the polymers.

3.1.2. Specifications

The specifications for polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) as defined in Commission Regulation (EU) No 231/2012 and by JECFA (2006a,b) are listed in Tables 2 and 4.

[12] 'PVP Polyvinylpyrrolidone polymers', commercial brochure by Ashland Specialities (2013). Available online: https://www.brenntag.com/media/documents/bsi/product_data_sheets/material_science/ashland_polymers/pvp_polymers_brochure.pdf

Table 2: Specifications for polyvinylpyrrolidone (E 1201) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation (EU) No 231/2012	**JECFA (2006a)**
Synonyms	Povidone; PVP; soluble polyvinylpyrrolidone	Povidone; PVP; INS No 1201
Definition	EINECS (EC) No: —	CAS No: 9003-39-8
	Chemical name: polyvinylpyrrolidone; poly-[1-(2-oxo-1-pyrrolidinyl)-ethylene]	Chemical names: polyvinylpyrrolidone; poly-[1-(2-oxo-1-pyrrolidinyl)-ethylene]
	Chemical formula: $(C_6H_9NO)_n$	Chemical formula: $(C_6H_9NO)_n$
	—	Structural formula: see Figure 1
	Molecular weight (g/mol): not less than 25,000 (average)	Formula weight (g/mol): lower molecular weight range product: about 40,000 higher molecular weight range product: about 360,000
	Assay: content not less than 11.5% and not more than 12.8% of nitrogen (N) on the anhydrous basis	Assay: not less than 12.2% and not more than 13.0% of nitrogen (N) on the anhydrous basis
Description	White or nearly white powder	White to tan powder; supplied in two molecular weight forms; the molecular weight value is an average molecular weight for the two forms
Identification	Solubility: soluble in water and in ethanol. Insoluble in ether	Solubility: soluble in water, in ethanol, and in chloroform. Insoluble in ether
	pH: between 3.0 and 7.0 (5% solution)	pH: 3.0–7.0 (5% solution)
	—	Precipitate formation: passes test[(a)]
Purity	Water content: not more than 5 % (Karl Fischer)	Water: not more than 5% (Karl Fischer method)
	—	Relative viscosity:[(a)] between 1.188 and 1.325 for lower molecular weight product, and between 3.225 and 5.662 for higher molecular weight product
	Total ash: not more than 0.1%	Total ash: not more than 0.02%
	Aldehyde: not more than 500 mg/kg (as acetaldehyde)	Aldehyde: not more than 0.2% (as acetaldehyde)[(a)]
	Free N-vinylpyrrolidone: not more than 10 mg/kg	Monomer content: not more than 1% (as vinylpyrrolidone)[(a)]
	Hydrazine: not more than 1 mg/kg	Hydrazine: not more than 1 mg/kg[(a)]
	Lead: not more than 2 mg/kg	Lead: not more than 2 mg/kg

(a): A specific test is directly available from the JECFA data sheet.

The Panel noted that Kollidon and Plasdone (Bühler, 2008) are additional synonyms for PVP used in pharmaceutical products and as test materials in toxicological studies.

The Panel noted that in the European Pharmacopoeia 9.0 (2017), the impurity 2-pyrrolidone has a limit of 3% whereas no limit for this impurity is set in the EU specifications. Information provided by the interested party (Documentation provided to EFSA n. 3) shows that the presence of 2-pyrrolidone ranges from [redacted] to [redacted] (Table 3). This compound could lead to the formation of an N-nitroso derivative, which is addressed in Section 3.6.4. The Panel considered that a limit for 2-pyrrolidone should be included in the EU specifications.

The Panel noted the following differences between JECFA and EU specifications: nitrogen content, 12.2–13.0% vs. 11.5–12.8%; the permitted amount of total ash, lower in JECFA specifications (0.02% vs. 0.1%). According to the empirical formula, PVP has a theoretical nitrogen content of 12.6% w/w and so the range of 11.5–12.8% in the EU specifications may be too broad to ensure acceptable purity. The Panel considered that the range for nitrogen content in the EU specifications should be revised based on the analytical data provided (Table 3).

[redacted] (PVP E 1201) [redacted] and [redacted] were analysed by the interested party (Documentation provided to EFSA n. 3, 2017) in 10 samples (five for each grade) of their products. A synopsis of the certificates of analysis available to EFSA was prepared by the Panel (Table 3).

Table 3: [redacted] (PVP E 1201) [redacted] and [redacted] results (except for nitrogen, for each parameter, the maximum analytical result obtained is shown together with, in parenthesis, the internal specification adopted in the study provided by the interested party, the regulatory specification and the specification of the European Pharmacopoeia) based on analytical certificates provided by Documentation provided to EFSA n. 3)

Parameter	[redacted]	[redacted]
Water content, %	[redacted] ≤ 5.0[(b),(c)])	[redacted] ≤ 5.0[(b),(c)])
pH (5% concentration in water)	[redacted] 3.0–7.0[(b),(c)])	[redacted] 3.0–7.0[(b),(c)])
Total ash (residue on ignition), %	[redacted] ≤ 0.1[(b),(c)])	[redacted] ≤ 0.1[(b),(c)])
Free N-vinylpyrrolidone, mg/kg	[redacted] ≤ 10[(b),(c)])	[redacted] ≤ 10.0[(b),(c)])
2-Pyrrolidone, %	[redacted] —[(b)]; ≤ 3.0[(c)])	[redacted] —[(b)]; ≤ 3[(c)])
Heavy metals (as lead), mg/kg[(e)]	[redacted] —[(b),(c)])	[redacted] —[(b),(c)])
Lead, mg/kg[(f)]	[redacted] ≤ 2[(b)] —[(c)])	[redacted] ≤ 2[(b)]; —[(c)])
Aldehydes (as acetaldehyde), mg/kg	[redacted] ≤ 500[(b),(c)])	[redacted] ≤ 500[(b),(c)])
Nitrogen, %	[redacted] 11.5–12.8[(b),(c)])	[redacted] 11.5–12.8[(b),(c)])
K-value (1% concentration in water)	[redacted] —[(b)]; 29–32[(c)])	[redacted] —[(b)]; 85–95[(c)])
Peroxide content, mg/kg	[redacted] —[(b)]; ≤ 400[(c)])	[redacted] —[(b)]; ≤ 400[(c)])
Hydrazine, mg/kg	[redacted] ≤ 1.0[(b),(c)])	[redacted] ≤ 1.0[(b),(c)])
Formic acid, %	[redacted] —[(b)]; ≤ 0.5[(c)])	[redacted] —[(b)]; ≤ 0.5[(c)])
Triethanolamine formate, %	[redacted] —[(b),(c)])	[redacted] —[(b),(c)])

(a): Internal specification reported in Documentation provided to EFSA n. 3.
(b): Specification in Commission Regulation (EU) No 231/2012 for polyvinylpyrrolidone as food additive (E 1201).
(c): Specification for Povidone in European Pharmacopoeia 9.0 (2017).
(d): No data available or requirement does not apply.
(e): Total Heavy metals = [Ag]+ [As]+ [Bi]+ [Cd]+ [Cu]+ [Hg]+ [Mo]+ [Pb]+ [Sb]+ [Sn] by ICP-OES; LODs/LOQs not reported.
(f): LOD/LOQ not reported.

The Panel noted that the peroxide, formic acid and triethanolamine formate contents were analysed in PVP, since there are limits in the EU Pharmacopeia (2017). The Panel noted that peroxide content is expressed as hydrogen peroxide. The Panel considered that limits for these compounds should be included also in the EU specifications for PVP (E 1201).

As already noted (Section 3.1.1) in the EU specifications, the term molecular weight (average) is used, while weight-average molecular weight is a more reflective terminology of its functional properties.

Table 4: Specifications for polyvinylpolypyrrolidone (E 1202) according to Commission Regulation (EU) No 231/2012 and JECFA (2006b)

	Commission Regulation (EU) No 231/2012	JECFA (2006b)
Synonyms	Crospovidone; cross-linked Polyvidone; insoluble polyvinylpyrrolidone	Insoluble polyvinylpyrrolidone; Crospovidone; cross-linked Polyvidone; insoluble PVP; polyvinylpolypyrrolidone; cross-linked homopolymer of 1-ethenyl-2-pyrrolidone; insoluble cross-linked homopolymer of N-vinyl-1-pyrrolidone; INS No 1202

	Commission Regulation (EU) No 231/2012	JECFA (2006b)
Definition	Polyvinylpolypyrrolidone is a poly-[1-(2-oxo-1-pyrrolidinyl)-ethylene], cross-linked in a random fashion. It is produced by the polymerisation of N-vinyl-2-pyrrolidone in the presence of either caustic catalyst or N,N′-divinyl-imidazolidone. Due to its insolubility in all common solvents, the molecular weight range is not amenable to analytical determination	A poly-[1-(2-oxo-1-pyrrolidinyl)-ethylene], cross-linked in a random fashion produced by the polymerisation of N-vinyl-2-pyrrolidone in the presence of either caustic catalyst or N,N′-divinyl-imidazolidone. Due to its insolubility in all common solvents, the molecular weight range is not amenable to analytical determination
	EINECS (EC) No: —	CAS No: —
	Chemical name: polyvinylpyrrolidone; poly-[1-(2-oxo-1-pyrrolidinyl)-ethylene]	—
	Chemical formula: $(C_6H_9NO)_n$	—
	Molecular weight (g/mol): —	—
	Assay: content not less than 11% and not more than 12.8% of nitrogen (N) on the anhydrous basis	Assay: not less than 11.0% and not more than 12.8% of nitrogen (N) calculated on the anhydrous basis
Description	A white hygroscopic powder with a faint, non-objectionable odour	White hygroscopic powder with a faint, non-objectionable odour
Functional uses	—	Colour stabiliser, colloidal stabiliser, clarifying agent
Identification	Solubility: insoluble in water, ethanol, and ether	Solubility: insoluble in water, ethanol, and ether
	PH: between 5.0 and 8.0 (1% suspension in water)	PH: 5.0–8.0 (1% w/v aqueous suspension)[(a)]
	—	Absorption of iodine: passes test[(b)]
Purity	Water content: not more than 6% (Karl Fischer)	Water: not more than 6% (Karl Fischer)
	Sulphated ash: not more than 0.4%	Sulphated ash: not more than 0.4%
	Water-soluble matter: not more than 1%	Water-soluble matter: not more than 1.5%[(b)]
	Free N-vinylpyrrolidone: not more than 10 mg/kg	Free N-vinylpyrrolidone: not more than 0.1 %[(b)]
	Free N,N′-divinyl-imidazolidone: not more than 2 mg/kg	Free N,N′-divinyl-imidazolidone: not more than 2 mg/kg[(b)]
	—	Zinc: not more than 25 mg/kg
	Lead: not more than 2 mg/kg	Lead: not more than 2 mg/kg

(a): In the JECFA data sheet, this specification comes under 'Purity'.
(b): A specific test is directly available from the JECFA data sheet.

In addition to the chemical name and synonyms shown in Table 4, Kollidon CL and Polyplasdone XL and Ultra are additional synonyms used to identify normal grades of pharmaceutical PVPP[13] (Documentation provided to EFSA n. 3; Bühler, 2008); the synonyms for fine/micronised powder grades are Kollidon CL-F, CL-SF and CL-M and Polyplasdone XL-10, Ultra 10 and INF-10. Other synonyms are Crospovidonum, cross-linked PVP and PVPP (Documentation provided to EFSA n. 2).

The Panel noted that both the EU and JECFA specifications are for nitrogen content, 11.0–12.8%. According to the empirical formula, PVPP has a theoretical nitrogen content of 12.6% w/w and so the range of 11.0–12.8% in the specifications may be too broad to ensure acceptable purity. The Panel noted that the range for nitrogen content in the EU specifications should be revised based on the analytical data provided (Table 5).

The Panel noted that in the JECFA specifications, a limit of 25 mg/kg is set for zinc, whereas in the EU specifications, zinc is not included. From the available information from the interested party on the manufacturing process, zinc is not used (Documentation provided to EFSA n. 3).

[13] Ashland (2014): 'Utility of Polyplasdone Crospovidone as a Superdisintegrant'. Available online: https://www.ashland.com/file_source/Ashland/Industries/Pharmaceutical/Links/PTR-097_Polyplasdone_crospovidone_as_a_Superdisintegrant.pdf

Samples of [redacted] (PVPP E 1202) products (five samples for each product) [redacted] and [redacted] were analysed by the interested party (Documentation provided to EFSA n. 3). A synopsis of the certificates of analysis available to EFSA was prepared by the Panel (Table 5).

Table 5: [redacted] (PVPP E 1202) products [redacted] and [redacted]: results (except for nitrogen, for each parameter, the maximum analytical result obtained is shown together with, in parenthesis, the internal specification adopted in the study provided by the interested party, the regulatory specification and the specification of the European Pharmacopoeia) based on analytical certificates provided by Documentation provided to EFSA n. 3)

Parameter	[redacted]	[redacted]	[redacted]
pH (1% suspension in water)	[redacted] 5.0–8.0[(b)]; —[(c)])	[redacted] 5.0–8.0[(b)]; —[(c)])	[redacted] 5.0–8.0[(b)]; —[(c)])
Loss on drying, %	[redacted] —[(b)]; ≤ 5.0[(c)])	[redacted] —[(b)]; ≤ 5.0[(c)])	[redacted] —[(b)]; ≤ 5.0[(c)])
Water content, %	[redacted] ≤ 6[(b)]; —[(c)])	[redacted] ≤ 6[(b)]; —[(c)])	[redacted] ≤ 6[(b)]; —[(c)])
Total ash (residue on ignition), %	[redacted] ≤ 0.4[(b)]; ≤ 0.1[(c)])	[redacted] ≤ 0.4[(b)]; ≤ 0.1[(c)])	[redacted] ≤ 0.4[(b)]; ≤ 0.1[(c)])
Water-soluble matter, %	[redacted] ≤ 1.0[(b)]; ≤ 1.5[(c)])	[redacted] ≤ 1.0[(b)]; ≤ 1.5[(c)])	[redacted] ≤ 1.0[(b)]; ≤ 1.5[(c)])
Free N-vinylpyrrolidone, mg/kg	[redacted] ≤ 10[(b),(c)])	[redacted] ≤ 10[(b),(c)])	[redacted] ≤ 10[(b),(c)])
Nitrogen, %	[redacted] 11.0–12.8[(b),(c)])	[redacted] 11.0–12.8[(b),(c)])	[redacted] 11.0–12.8[(b),(c)])
Adsorptive activity, %	[redacted]	[redacted] —[(b),(c)])	[redacted]
Peroxide content, mg/kg	[redacted] —[(b)]; ≤ 400[(c)])	[redacted] —[(b)]; ≤ 400[(c)])	[redacted] —[(b)]; ≤ 400[(c)])
Heavy metals (as lead), mg/kg[(e)]	[redacted] ≤ 2 lead[(b)]; —[(c)])	[redacted] ≤ 2 lead[(b)]; —[(c)])	[redacted] ≤ 2 lead[(b)]; —[(c)])
Arsenic, mg/kg[(f)]	[redacted] —[(b),(c)])	[redacted] —[(b),(c)])	[redacted] —[(b),(c)])
Free N,N′-divinyl-imidazolidone, mg/kg	[redacted] ≤ 2[(b)]; —[(c)])	[redacted] ≤ 2[(b)]; —[(c)])	[redacted] ≤ 2[(b)]; —[(c)])

(a): Internal specification reported in Documentation provided to EFSA n. 3.
(b): Specification in Commission Regulation (EU) No 231/2012 for polyvinylpolypyrrolidone as food additive (E 1202).
(c): Specification for Crospovidone in European Pharmacopoeia 9.0 (2017).
(d): Data unavailable or requirement does not apply.
(e): Total Heavy metals = [Ag]+ [As]+ [Bi]+ [Cd]+ [Cu]+ [Hg]+ [Mo]+ [Pb]+ [Sb]+ [Sn] by ICP-OES; LODs/LOQs not reported.
(f): LOD/LOQ not reported.

No data were provided for the analysis of samples of PVPP (E 1202) for 2-pyrrolidone, whereas samples of PVP (E 1201, Table 3) were reported to contain up to [redacted]. The Panel considered that the presence of 2-pyrrolidone as an impurity in PVPP is likely given that both PVP and PVPP are made from the same starting monomer. The Panel noted that, in contrast to PVP, the pharmacopoeia does not contain an impurity limitation for 2-pyrrolidone in PVPP. As well as including a limit value for 2-pyrrolidone for PVP (E 1201), the Panel also recommend a limit value in the EU specifications for PVPP (E 1202).

The Panel noted that the levels of arsenic were monitored although this substance is not present in the regulatory specifications for PVPP (E 1202), whereas N,N′-divinylimidazolidone was not analysed. With regard to this chemical, the Panel noted that, according to the information from the interested party, the manufacture of polyvinylpolypyrrolidone is only carried out in the presence of a caustic catalyst (see Section 3.1.3) but that polyvinylpolypyrrolidone can also be manufactured using N,N′-divinyl-imidazolidone (Documentation provided to EFSA n. 6,3).

The interested party provided a report on the determination of particle size distribution from scanning electron microscopy (SEM) images using the Malvern Morphologi G3 software; the evaluation concerned three samples of PVP (E 1201) and seven samples of PVPP (E 1202) (Documentation provided to EFSA n. 4). The report mentioned that 'the SEM images provided were not ideal for this purpose, with numerous particles too close to be distinguished as individual and oftentimes without enough contrast to the background, which made setting thresholds difficult'. The Panel agreed with this observation and noted that the materials were highly agglomerated, forming 'near-spherical' agglomerates, and therefore, individual constituent particle sizes were not determinable measured.

Because small particles were observed in the electron micrographs, it is questionable whether the lower limit of quantification (LLOQ) determined by the choice of magnifications (pixel size) allowed precise measurement of isolated particles in the nano range. Based on the data submitted, the Panel could not exclude the presence of nano-sized particles in the analysed materials. Therefore, the Panel considered that appropriate data on the potential presence of nanoparticles in PVP (E 1201) and PVPP (1202) should be provided. The data should be generated in accordance with the EFSA Guidance (2018) and following the principle outlined in the latest Guidance (add the link of the latest one for PC), prior to consideration on the need for inclusion of particle size distribution as an additional parameter in the EU specifications.

The Panel noted that the peroxide content was analysed in PVP (E 1201) and PVPP (E 1202), since there is a limit in the EU Pharmacopeia (2017), and considered that a limit for peroxide content should be included also in the EU specifications for both food additives.

The Panel noted that, according to the EU specifications for polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202), the impurity of the toxic element lead is accepted up to a concentration of 2 mg/kg. The Panel noted that the levels of lead should be kept as low as possible.

Based on analytical data provided by the interested party for PVP and PVPP (Documentation provided to EFSA n. 3), the Panel further noted that several elements of toxicological importance were analysed in addition to lead: arsenic, cadmium, chromium, cobalt, copper, mercury and nickel have been reported [redacted]. The Panel noted that limits for the aforesaid elements should be included in the regulatory specifications.

In light of the above observations, the Panel considered that the EU specifications for PVP (E 1201) and PVPP (1202) should be revised in order to include better definitions and assays.

3.1.3. Manufacturing process

Polyvinylpyrrolidone

Soluble polyvinylpyrrolidone polymers (PVP hereafter) are obtained by free-radical polymerisation of N-vinyl-2-pyrrolidone (VP) in high purity water, yielding the chain structure exhibited in Figure 1. Hydrogen peroxide, ammonium hydroxide (NH_4OH) and copper solution catalyse the reaction (Documentation provided to EFSA n. 3). [redacted]

[redacted]

Polyvinylpolypyrrolidone

According to the EU specifications, insoluble polyvinylpyrrolidone is produced by the polymerisation of N-vinyl-2-pyrrolidone in the presence of either caustic catalyst or N,N'-divinyl-imidazolidone.

The interested party (Documentation provided to EFSA n. 2) stated that they only manufacture E1202 using sodium hydroxide as a catalyst. [redacted] It is produced by the exothermic polymerisation reaction of vinyl pyrrolidone (VP) using sodium hydroxide in cold deionised water. [redacted] After a second stage filter, the wet cake is diluted and spray dried. The powder can be directly packaged or milled to a smaller particle size. Some products are packaged in nitrogen atmosphere to minimise peroxide formation (Documentation provided to EFSA n. 3).

The Panel noted that according to the information provided by the interested party (Documentation provided to EFSA n. 2), N,N'-divinyl-imidazolidone is used as a catalyst by other manufacturers; however, no information has been submitted to EFSA.

3.1.4. Method of analysis in food

No specific methods of analysis of PVP (E 1201) and PVPP (E 1202) in food have been made available to the Panel following EFSA's call for data. Based on indications provided by the interested party (Documentation provided to EFSA n. 1, 2019), analytical methods can be adapted from those developed for testing PVP and PVPP in pharmaceutical preparations, described in Bühler (2008). What follows is a synthetic description of these methods.

Polyvinylpyrrolidone

Means of detecting PVP grades in pharmaceutical preparations — in solid dosage form such as tablets, granules, capsules and coated tablets — are available from the report by Bühler (2008). Sample extraction (e.g. with trichloroethylene) is followed separation steps to isolate the fraction containing PVP (and possibly PVPP). However, it is generally understood that the best method to deal with a specific case can only be determined by trial with the matrix involved. PVP and PVPP can be detected separately in the semi-purified extract if the latter is subject to thin layer chromatography on silica gel or paper using a suitable eluent; the chromatogram is then sprayed with Lugol's iodine solution for colour development. Electrophoresis can also be used to detect PVP in the presence of PVPP.

The most versatile method for quantitatively determining PVP grades with sufficient accuracy is likely the photometric measurement of the PVP-iodine complex, a method that was successfully tested on samples that also contained a series of auxiliaries and active ingredients. Diphenhydramine, ethylpapaverine, phenylbutazone, ascorbic acid and starch react with iodine, therefore, the general method in which iodine is used as a reagent must be modified by pretreating the samples to enable PVP to be determined in solutions that contain these substances.

A UV spectrophotometric determination of PVP K-30 in solid dispersions and physical mixtures with active ingredients was developed by multicomponent analysis (Bühler, 2008). Because the UV absorbance spectra of PVP were completely overlapped by the UV absorbance spectra of the matrix, a direct spectrophotometric determination of PVP was impossible. However, UV spectrophotometric data were analysed by a software for quantitative multicomponent analysis using chemometrics and optimised experimental conditions (solutions buffered at pH 7.4). A reliable detection of PVP was obtained when the PVP content in the powder sample exceeded 20 % (w/w).

Polyvinylpolypyrrolidone

Gravimetric analysis appears to be the best method for the quantitative determination of PVPP in preparations. The sample material is suspended in water and/or a suitable solvent that dissolves all the other components of the preparation. PVPP is determined gravimetrically after filtration and drying (at 105°C for 3 h).

3.1.5. Stability of the substance, and reaction and fate in food

Polyvinylpyrrolidone

The interested party provided evidence for stability of [redacted] (PVP E 1201) [redacted] and [redacted] over 24- and 36-month storage periods, respectively (Documentation provided to EFSA n. 3). For the test, samples of five [redacted] and six [redacted] batches were stored in a variety of standard commercial shipping containers at ambient temperature and humidity; samples were kept in defined locations in the warehouse where the commercial product was normally stored. During storage, for the stability study, several parameters were checked at different times. Except for peroxides, results were compliant with the target limits that were originally set for the stability tests, in line with pharmacopoeian requirements and, where it applies, with the EU specifications for E 1201 (Table 3). In test samples, the peroxide content was found to remain substantially stable or eventually increase slowly with elapsing time, in general remaining within the pharmacopoeian requirement of 400 mg H_2O_2/kg (European Pharmacopoeia 9.0, 2017) over the observation periods. However, in three batches of [redacted], the level of peroxides was found to increase above the target limit of 400 mg H_2O_2/kg in the last part of the 24-month test, reaching levels of [redacted].

Polyvinylpolypyrrolidone

As reported by the interested party, the shelf-life of various [redacted] (PVPP E 1202) products was investigated for 24 months at room temperature (Documentation provided to EFSA n. 3). The products tested were [redacted] and [redacted] (21 batches in all), and [redacted] and [redacted] (eight batches in all). [redacted] batches were stored in a variety of standard commercial shipping containers at ambient temperature and humidity; samples were kept in defined locations in the warehouse where the commercial product was normally stored. During storage, for the stability study, various parameters were checked at different times. Except for peroxides and occasional minor exceedances of the water-soluble matter, results were compliant with the target limits that were originally set for the stability tests, in line with pharmacopoeian requirements and, where it applies, with regulatory specifications for E 1202 (Table 5). In test samples, the peroxide content was in general found to remain within the pharmacopoeian requirement of 400 mg H_2O_2/kg (European Pharmacopoeia 9.0, 2017) over the observation periods of 24 months. However, in few batches of [redacted] and [redacted], the level of peroxides was found to increase above the target limit of 400 mg H_2O_2/kg in the last part of the test, reaching levels of [redacted]. The shelf-life testing of [redacted] and [redacted] products was stretched to 36 months with, however, inconsistent results when compared with the target limits of the study.

The Panel noted that the levels of peroxides detected in shelf-life testing trials are exceeding the pharmacopoeian requirement (400 mg H_2O_2/kg) in some PVP and PVPP batches. According to the interested party (Documentation provided to EFSA n. 2), all PVP and PVPP products are known to form peroxides over time upon prolonged exposure to heat and oxygen: once the product package is opened, the autoxidation process inevitably starts, and peroxides increase over time. The interested party clarified that during the stability studies submitted in 2017 on different batches of the same product, the packaging was repeatedly opened to collect and analyse product samples: any variation in sampling and packaging re-sealing had likely an effect on future peroxide levels in the batch. It has also been stated that the studies were also performed in normal warehouse ambient conditions, where the temperature and humidity could vary considerably. Inert packaging and oxygen impermeable liners with an ethylene vinyl alcohol barrier layer for all pharma and food grade PVP [redacted] products have been implemented and the result was a marked improvement in peroxide stability.

3.2. Authorised uses and use levels

Maximum levels of PVP (E 1201) and PVPP (E 1202) have been defined in Annex II to Regulation (EC) No 1333/2008[14] on food additives, as amended. In this document, these levels are named maximum permitted levels (MPLs).

Currently, PVP (E 1201) and PVPP (E 1202) are authorised as food additives in the EU at *quantum satis* (QS) in the two food categories listed in Table 5.

Table 6: MPLs of PVP (E 1201) and PVPP (E 1202) in foods according to the Annex II to Regulation (EC) No 1333/2008

Food category number	Food category name	E-number/ Group	Restrictions/ exception	MPL (mg/L or mg/kg as appropriate)
11.4.3	Table top sweeteners in tablets	E 1201/ E 1202		*Quantum satis*
17.1	Food supplements supplied in a solid form, excluding food supplements for infants and young children	E 1201/ E 1202	Only foods in tablet and coated tablet form	*Quantum satis*

MPL: maximum permitted level.

PVP (E 1201) and PVPP (E 1202) are also authorised according to Annex III, Part 1 of Regulation (EC) No 1333/2008, as carrier in sweeteners[15] at *QS*. This means that these food additives can be present in foods containing sweeteners.

PVPP (E 1202) is also authorised as clarifying agent (processing aid), at a level of no more than 80 g/hL (800 mg/L) according to Regulation No 934/2019 in different categories of wine products (wine, liqueur wine, sparkling wine, quality sparkling wine, quality aromatic sparkling wine, aerated sparkling wine, semi-sparkling wine, aerated semi-sparkling wine, grape must, wine from raisined grapes, wine of overripe grapes).

The Panel noted that PVPP as processing aid is also used in the production of beers (Dostálek et al., 2011).

Neither uses were considered in the exposure assessment.

3.3. Exposure data

3.3.1. Reported use levels or data on analytical levels of polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202)

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives with MPL at *QS*.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued a public call[16] for occurrence data (usage level and/or concentration data) on PVP (E 1201) and PVPP (E 1202). In response to this public call, updated information on the actual use levels of both additives was made available to EFSA by industry. No analytical data of the two additives in foods were provided by the Member States.

Summarised data on reported use levels of polyvinylpyrrolidone (E 1201) in foods provided by industry

Industry provided EFSA with 35 use levels of PVP (E 1201) in food supplements (FC 17). These data were made available to EFSA by Ashland Specialties (Documentation provided to EFSA n. 9), Food Supplement Europe (FSE) (Documentation provided to EFSA n. 7), Dr Loges Naturheilkunde neu entdecken (LOGES) (Documentation provided to EFSA n. 11), the Association of the European Self-

[14] 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.

[15] The sweetener preparations covered by the provisions of Annex III Part 1 with respect to the use of carriers, concern sweetener preparations to be used by food manufactures (and not the final consumer).

[16] https://www.efsa.europa.eu/en/data/call/170223

Medication Industry (AESGP) (Documentation provided to EFSA n. 8) and Nathura (Documentation provided to EFSA n. 10).

The Panel noted that one data provider, namely Ashland Specialties (Documentation provided to EFSA n. 9) was a chemical supplier that does not directly use this substance as additive in foods. Use levels reported by food additive producers are therefore not considered at the same level as those provided by food industry. Food additive producers might recommend use levels to the food industry but the final levels used might, ultimately, be different. Therefore, unless food additive producers confirm that the recommended levels are used by food industry, they are not considered in the refined exposure scenario. Data from food additive producers will only be used in the *maximum level exposure assessment* scenario in case of QS authorisation when no data are available from food industry. In this way, the most complete exposure estimates are calculated. Since actual use level data from food industry were available, the data from the food additive producer were not used in the exposure assessment of PVP (E 1201).

Appendix A.1 provides data on the use levels of PVP (E 1201) in food supplements as reported by industry.

Summarised data on reported use levels of polyvinylpolypyrrolidone (E 1202) in foods provided by industry

Industry provided EFSA with 16 use levels of PVPP (E 1202) in food supplements (FC 17).

Updated information on the actual use levels of PVPP (E 1202) in foods was made available to EFSA by Ashland Specialities (Documentation provided to EFSA n. 9), the Association of the European Self-Medication Industry (AESGP) (Documentation provided to EFSA n. 8) and Nathura (Documentation provided to EFSA n. 10).

Also for PVPP (E 1202), one data provider, namely Ashland Specialties (Documentation provided to EFSA n. 9), was a chemical supplier. Since actual use level data from food industry were also available for PVPP (E 1202), the data from Ashland Specialties (Documentation provided to EFSA n. 9) were not used in the exposure assessment.

Appendix A.2 provides data on the use levels of PVPP (E 1202) in food supplements as reported by industry.

3.3.2. Summarised data extracted from the Mintel's Global New Products Database

The Mintel's GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 3.1 million food and beverage products of which more than 1,100,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 20 out of its 28 member countries and Norway presented in the Mintel GNPD.[17]

For the purpose of this Scientific Opinion, Mintel's GNPD[18] was used for checking the labelling of food and beverages products and food supplements for PVP (E 1201) and PVPP (E 1202) within the EU's food market as the database contains the compulsory ingredient information on the label.

According to Mintel's GNPD, PVP (E 1201) was labelled on a few products (n = 286) belonging to the food subcategories of Mintel's GNPD food classification 'Vitamins & dietary supplements', 'Medicated confectionery' and 'Energy drinks' between January 2015 and January 2020. PVPP (E 1202) was labelled on 109 products belonging to the food subcategory 'Vitamins & dietary supplements' and only two products of the food subcategory 'Beer' between January 2015 and January 2020.

Appendices B.1 and B.2 list the percentage of the foods labelled with PVP (E 1201) and PVPP (E 1202) out of the total number of food products per food subcategory with at least one food labelled to contain these additives according to the Mintel's GNPD food classification. The average percentage of foods labelled to contain the additives among the food subcategories with at least one food labelled to contain PVP (E 1201) and PVPP (E 1202) was 2.2% and 0.5%, respectively.

3.3.3. Food consumption data used for the exposure assessment

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the

[17] Missing Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta and Slovenia.
[18] http://www.gnpd.com/sinatra/home/ accessed on 15/1/2020.

individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a). Consumption surveys added in the Comprehensive Database in 2015 were also taken into account in this assessment.[19]

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons may not be appropriate. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database includes the currently best available food consumption data across Europe.

Food consumption data of children, adolescents, adults and the elderly were used for the exposure assessment. For the present assessment, food consumption data were available from 13 different dietary surveys carried out in eight European countries (Table 7). Infants and toddlers were not included in the assessment (see Section 3.4).

Table 7: Population groups considered for the exposure estimates of PVP (E 1201) and PVPP (E 1202)

Population	Age range	Countries with food consumption surveys covering more than 1 day
Children[(a)]	From 36 months up to and including 9 years of age	Finland, Germany, Italy, Netherlands, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Finland, Germany, Italy, Netherlands, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Finland, Ireland, Italy, Netherlands, Romania, UK
The elderly[(a)]	From 65 years of age and older	Finland, Ireland, Italy, Netherlands, UK

(a): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).

Consumption records were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the food categorisation system (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform the exposure assessment. In practice, the FoodEx food codes were matched to the FCS food categories.

Food categories considered for the exposure assessment of polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202)

Use levels of PVP (E 1201) and PVPP (E 1202) were provided for food supplements. Consumption levels of these supplements were selected from the Comprehensive Database (FoodEx classification system). The additives are only authorised in FC 17.1, food supplements in tablet and coated tablet form (Table 6). This restriction could not be taken into account in the exposure assessment, because the Comprehensive Database does not contain information about the form of the supplement consumed. The exposure assessment included therefore all food supplements irrespective of the form (FC 17.1 and 17.2).

No use levels were provided for FC 11.4.3. 'Table top sweeteners in tablets'. This food category was therefore not included in the exposure assessment (Appendix C).

3.4. Exposure to polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202) from their use as food additives

The Panel estimated the chronic dietary exposure to PVP (E 1201) and PVPP (E 1202) for the following population groups: children, adolescents, adults and the elderly. The FAF Panel estimated the exposure to both PVP (E 1201) and PVPP (E 1202) using the *food supplements consumers only scenario*, because use levels were only reported for food supplements (FC 17). This scenario is based on consumers only of food supplements, which are assumed to be exposed to the food additive at the maximum reported use level in food supplements on a daily basis.

Dietary exposure to PVP (E 1201) and PVPP (E 1202) was calculated by multiplying the maximum reported use level of each food additive for food supplements (Appendix C) with the consumed

[19] Available online: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

amount of these supplements per kilogram body weight for each individual in the Comprehensive Database. The exposure was calculated for consumers who reported the consumption of food supplements on at least one day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only 1 day per subject were excluded as they are considered not adequate to assess repeated exposure.

The exposure was calculated per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 7). Based on these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. The 95th percentile of exposure was only calculated for those population groups with a sufficiently large sample size (EFSA, 2011a).

As FC 17 does not consider food supplements for infants and toddlers as defined in the legislation, the exposure to PVP (E 1201) and PVPP (E 1202) from food supplements was not estimated for these two population groups.

A possible additional exposure from the use of PVP (E 1201) and PVPP (E 1202) as food additives in sweeteners in accordance with Annex II and III to Regulation (EC) No 1333/2008 (Part 1) was not considered as no concentration data were available reflecting this use. The authorised use of PVPP (E 1201) as an oenological practice was also not considered for the same reason.

Dietary exposure to polyvinylpyrrolidone (E 1201) and to polyvinylpolypyrrolidone (E 1202)

Table 8 summarises the estimated exposure to PVP (E 1201) and PVPP (E 1202) from their use as food additives in four population groups (Table 7) according to the food supplements consumers only exposure scenario. Detailed results per population group and survey are presented in Appendices D.1 and D.2.

Table 8: Summary of dietary exposure to PVP (E 1201) and to PVPP (E 1202) from their use as food additives in the food supplements consumers only exposure scenario, in four population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
E 1201: Food supplement scenario consumers only				
• Mean	1.7–17.6	1.3–4.1	0.6–4.3	1.6–4.7
• 95th percentile	6.3–23.7	3.1–5.2	3.7–21.1	5.0–17.9
E 1202: Food supplement scenario consumers only				
• Mean	1.8–18.6	1.4–4.3	0.6–4.5	1.7–4.9
• 95th percentile	6.7–25.0	3.3–5.5	3.9–22.3	5.3–18.9

The mean exposure to PVP (E 1201) from its use as a food additive ranged between 0.6 mg/kg bw per day for adults and 17.6 mg/kg bw per day for children. The 95th percentile of exposure to PVP (E 1201) ranged for between 3.1 mg/kg bw per day for adolescents and 23.7 mg/kg bw per day and for children.

The mean exposure to PVPP (E 1202) from its use as a food additive ranged between 0.6 mg/kg bw per day for adults and 18.6 mg/kg bw per day for children. The 95th percentile of exposure to PVPP (E 1202) ranged between 3.3 mg/kg bw per day for adolescents and 25.0 mg/kg bw per day for children.

Uncertainty analysis

Uncertainties in the exposure assessment of PVP (E 1201) and PVPP (E 1202) have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised in Table 9.

Table 9: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction[(a)]
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/–
Methodology used to estimate high percentiles (95th) of long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
Uncertainty in possible national differences in use levels of food categories	+/–
Concentration data: use levels considered applicable to all foods within the entire food supplements category, whereas on average 2.3% and 0.4% of the food supplements were labelled with PVP (E 1201) and PVPP (E 1202), respectively	+
The one food category which was taken into account in the Food supplements consumers only scenario out of the two authorised food categories, corresponded to 12% to 100% of the amount (g of foods by body weight) of food consumption documented in the EFSA Comprehensive Database	–
Food category selected for the exposure assessment: inclusion of food category without considering the restriction/exception (n=1/2)	+
Food supplements consumers only scenario: – exposure calculations based on the maximum reported use from industries	+

(a): +, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

PVP (E 1201) and PVPP (E 1202) are authorised in two food categories according to Annex II to Regulation No 1333/2008 one of which is food supplements (FC 17). This category was the only one considered in the current exposure assessment for both additives according to a consumers' only scenario. According to Mintel's GNPD (Appendices B.1 and B.2), PVP (E 1201) and PVPP (E 1202) are labelled on foods belonging to three food subcategories. The subcategory 'Vitamins & Dietary Supplements', the only one considered in the current assessment, represented approximately 99% and 98% of the food products labelled with PVP (E 1201) and PVPP (E 1202) in Mintel's GNPD, respectively. The only other subcategory in which PVPP (E 1202) was labelled was 'Beers', but that use was very minor (n = 2). Furthermore, the percentage of supplements within the subcategory Vitamins & Dietary Supplements labelled to contain PVP (E 1201) or PVPP (E 1202) out of the total number of foods within this subcategory was maximally about 2.8% and 1.1%, respectively (Appendices B.1 and B.2), while in the assessment, it was assumed that 100% of the food supplements contained the additives. Furthermore, it was assumed that all supplements contained the additives at the maximum reported use level.

Given these observations, the Panel considered overall that the uncertainties identified resulted in an overestimation of the exposure to PVP (E 1201) and PVPP (E 1202) from their use as food additives according to Annex II. The Panel noted that food categories which may contain the additives due to carry-over (Annex III, Part 1, to Regulation (EC) No 1333/2008) were not considered in the current exposure assessment. This use could result in an underestimation of the exposure. The presence of PVPP in must, wine and wine products, and beers due to its use as a processing aid is anticipated to be negligible owing to the employed filtration step during the production processes of these beverages.

3.5. Proposed extension of use for polyvinylpyrrolidone (E 1201)

A request for an extension of use for PVP (E 1201) was also considered. The request referred to the use in foods for special medical purposes (FSMP) in tablet and coated tablet form i.e. FC 13.2 of part E of Annex II to Regulation (EC) No 1333/2008 at a proposed maximum use level of 44,500 mg/kg (Documentation provided to EFSA n.39).

Eating occasions related to this food category are not available in the EFSA Comprehensive Database. To estimate the potential exposure to PVP (E 1201) from this use, an average daily consumption of two tablets was assumed, as recommended by the applicants. The concentration of PVP (E 1201) per tablet is indicated to be 50 mg/tablet. The exposure for consumers of foods for special medical purposes (FC 13.2) would therefore be 100 mg per day. For adults, the exposure would be 1.4 mg/kg bw per day based on a body weight of 70 kg, for adolescents, it would represent 1.9 mg/kg bw per day based on a body weight of 53 kg and for children, 4.3 mg/kg bw per day based on a body weight of 23 kg.

If individuals consuming food supplements (FC 17) containing PVP (E 1201) at the reported maximum use level would also consume the FSMP tablets (FC 13.2), the mean exposure to PVP (E 1201) would be up to 21.9 mg/kg bw per day for children, 6 mg/kg bw per day for adolescents and 5.7 and 6.1 mg/kg bw per day for adults and the elderly, respectively.

3.6. Biological and toxicological data

This section summarises the biological and toxicological studies for which the original reports have been provided by the interested party (Documentation provided to EFSA n. 5). No additional studies have been identified in the open literature.

The Panel noted that the parameters and maximum limits established in the EU specifications for PVP and PVPP (except for lead and free N,N'-divinyl-imidazolidone) are included in the specifications for the pharmaceutical-grade products (European Pharmacopoeia 9.0, 2017). Therefore, the tested material(s) in toxicological studies complying with Pharmacopoeia meet also the EU specifications for E1201 and E1202.

According to the interested party (Documentation provided to EFSA n. 6), PVPP (indicated as Kollidon® (BASF) used in some of the toxicological studies, would likely have been produced using N, N'-divinylimidazolidone rather than sodium hydroxide.

3.6.1. Absorption, distribution, metabolism and excretion

Polyvinylpyrrolidone (PVP)

Rats

In order to determine the metabolic fate of PVP after oral exposure, albino rats (N = 4, sex and body weight not specified) received by gavage 10% water solution of radioactive (^{14}C) PVP K-90 (Industrial Biology Research and Testing Laboratories, 1960; Documentation provided to EFSA n. 12). Essentially all (97.1%) of the administered dose was found in the faeces and urine after 168 h. About 0.35% of the ^{14}C dose was excreted in the urine in the first 13 h, and much smaller quantities continued to appear in the urine for at least 5 days. About 0.04% of the dose was converted to carbon dioxide in the exhaled air in the first 6 h. The gastrointestinal tract and the liver showed small traces of radioactivity while PVP was not detected in kidneys, spleen and brain.

In order to determine the metabolic fate of PVP after oral exposure, albino rats (N = 5, sex and body weight not specified) received by gavage radioactive (^{14}C) PVP K-30 (Industrial Toxicology Laboratories, 1953; Documentation provided to EFSA n. 13). About 99% of the administered ^{14}C PVP was excreted in faeces mostly during the first day, approximately 1% in the urine and 0.25% in exhaled carbon dioxide. The internal organs (lungs, liver, kidneys and spleen from four rats) contained less than 0.001% of the radioactivity. The maximum amount of radioactivity in the entire body was less than 0.5% of the administered dose after 5 days.

Polyvinylpolypyrrolidone (PVPP)

Rats

In a study of absorption and excretion, rats (two male rats in preliminary study and three males and three females in the main study, four males in a biliary excretion study; the strain not specified), received by gavage a single dose of approximately 1 mg of PVPP labelled with ^{14}C/kg bw (range from 0.7 to 1.4 mg/kg bw depending on an individual body weight of the rats in each study) (Associated Technical Services, 1979; Documentation provided to EFSA n. 14). About 0.13% of the administered ^{14}C dose was absorbed. The major portion of the administered dose was excreted in the first 24 h. Excretion of radioactivity was practically completed after 48 h. Urinary excretion accounted for approximately 0.1% and biliary excretion for approximately from 0.003% to 0.008% of the administered dose. The fraction remaining in the organism 48 h post-dosing corresponded to approximately 0.1% of the initial dose.

In another study of oral absorption and excretion, single doses of ^{14}C labelled PVPP (dose not specified) were administered by gavage to Sprague Dawley rats (males weighing 200–300 g, N = 5 per each time of sacrifice performed 6, 12, 24 and 48 h post-dosing) (Digenis, 1979; Documentation provided to EFSA n. 15). Less than 1% of the total ^{14}C dose was detected in the organs analysed (spleen, kidneys, liver, lungs, thymus, adrenal glands), blood and urine at each time point. According

to the summary of the results, the radioactivity in faeces accounted for 63.7, 70.5 and 74.5% after 12, 24 and 48 h, respectively.

Overall, the studies with radiolabelled PVP or PVPP in laboratory rats indicate low intestinal absorption of these compounds as only trace amounts of the radiolabel were detected in the organs while majority of the dose was found in the faeces. The small amount which becomes systemically available is mainly eliminated via kidney.

3.6.2. Acute toxicity

In a review by Robinson et al. (1990), the reported oral LD50 of PVP (K values not specified) was in rats between 40,000 and 100,000 mg/kg bw, in mice 40,000 mg/kg bw and in guinea pig 100,000 mg/kg bw. In rabbits given by gavage single doses of PVP (K value of 30 approximately, based on MW of 50,000) amounting to 2,700 mg PVP/kg bw, no test compound-related effects were reported apart from a slight inhibition of body weight gain (Neuman et al., 1979 as cited in a review by Robinson et al., 1990).

The reported oral LD50 value of PVPP (Crospovidone, 1-vinyl-2-pyrrolidone homopolymer) was higher than 7,000 mg/kg bw in mice and rats (The Center of Japan Biological Chemistry, 1984; Documentation provided to EFSA n. 16) and higher than 5,000 mg/kg bw in beagle dogs (Fuji Life Science Incorporated, Funahashi et al. 1985; Documentation provided to EFSA n. 17).

The Panel considered PVP and PVPP to be of low acute toxicity.

3.6.3. Short-term and subchronic toxicity

Polyvinylpyrrolidone (PVP)

Rats

Two groups, each of 10 male and 10 female Sprague-Dawley rats received 2.5 or 5% PVP (K-90, Kollidon 90, equivalent to 3,000 or 6,000 mg/kg bw per day) in a basal diet (Altromin R) for 28 days (BASF, 1977; Documentation provided to EFSA n. 18). Two control groups (10 rats/sex per group) were used. The first control was kept on the basal diet and the second one on the basal diet supplemented with 5% (w/w) cellulose. Body weight of all test groups was comparable to that in the control group fed the basal diet. Feed intake in groups on diet with 5% cellulose, 2.5 and 5% of PVP (K-90) was comparable to that in the control fed the basal diet. Haematological, clinical chemistry examinations, urinalysis, necropsy, organ weights and histological examination did not reveal any changes compared to control, which could be attributed to the test compounds. No accumulation of PVP (K-90) was seen by microscopy in mesenteric lymph nodes.

Groups of 25 male and 25 female albino rats of the Sherman Wistar strain were exposed via the diet to 10% PVP (K-90) (group I); 5% PVP (K-90, group II); 2% PVP (K-90, group III) or 0% PVP (K-90, control group IV) (equivalent to 9,000, 4,500, 1,800 or 0 mg/kg bw per day, respectively) for 90 days (Industrial Biology Research and Testing Laboratories, 1959; Documentation provided to EFSA n. 19). Haematology parameters (RBC count; WBC count; Hb and differential count) were determined in five males and five females of each group at the beginning and at the end of the 90-day treatment period. At the end of the study, all rats were sacrificed. Gross and microscopic examination was performed of five male and five female rats of each group. Special staining techniques for PVP (K-90) were used on the tissues (stomach, intestine, pancreas, liver, heart, spleen, lung, kidney, gonads, brain and mesenteric lymph nodes) of 10 animals of each group, which were examined microscopically. Growth, haematology and gross and microscopic examination did not reveal any effect related to the treatment with PVP (K-90). In addition, PVP (K-90) was not detected in the organs and tissues examined. The Panel considered the NOAEL from this study to be 10% (equivalent to 9,000 mg/kg bw per day) PVP (K-90), the highest dose tested.

Rabbits

NZW rabbits (5/sex per group, age between 6 and 7 months, the initial body weight between 2.1 and 2.7 kg) received by gavage 300, 900 or 2,700 mg PVP (average molecular weight 50,000, as reported by the authors)/kg bw per day for 4 weeks (Laboratorium fur Pharmakologie und Toxikologie, 1979; Documentation provided to EFSA n. 20). A control group (5/sex) received distilled water. The dosing volume was 20 mL/kg bw. Statistically significant differences from the control group were recorded in the high-dose PVP group: slightly lower body weight gain, decreased α_1-globulin and a slightly increased γ-globulin at the end of the treatment. According to the authors, the changes in the

two clinical chemistry parameters were within the biological range. The absolute (but not the relative) liver weight in the high-dose group was statistically significantly lower than that in the control group. Microscopic examination of the liver revealed no changes that could be related to treatment at any PVP dose tested. The Panel considered the NOAEL in this study to be 2,700 mg PVP/kg bw per day, the highest dose tested.

Dogs

Three groups, each of four male and four female beagle dogs (6.5 months old, initial body weight of males 8.5–13.6 kg and of females 8.1–12.6 kg) received 2.5, 5% or 10% PVP (K-90, Kollidon 90) (equivalent to 625, 1,250 or 2,500 mg/kg bw per day) in a basal diet for 28 days (BASF, 1977; Documentation provided to EFSA n. 21). Two control groups (4/sex per group) were used: the untreated control kept on the basal diet and the 'cellulose control' kept on the basal diet added 10% cellulose. The dogs administered PVP (K-90) had occasionally loose stool and diarrhoea and three males and one female in the high-dose PVP group had a slightly, but not statistically significantly, lower body weights as compared to those in other groups. Haematology and urinalysis parameters were not affected by the treatment. Clinical chemistry examination revealed a statistically significant increase in urea and a statistically significant decrease in total lipids in high-PVP dose females. No difference between the treated and control animals was seen at necropsy, in organ weights and by histological examination of the organs, except for a statistically significant increased relative weight of spleen in the high-dose PVP females only. Considering that the above-mentioned statistically significant findings were not of toxicological relevance, the Panel identified the NOAEL form this study to be 10% PVP (K-90) (equivalent to 2,500 mg PVP K-90/kg bw per day), the highest dose tested.

Groups of two male and two female Beagle dogs were exposed via the diet for 90 days to 10% PVP (K-90, group I); 5% PVP (K-90, group II); 2% PVP (K-90, group III) or 0% PVP (K-90, control group IV). All animals were weighed weekly during the entire period of the experiment (Industrial Biology Research and Testing Laboratories, Inc., 1958; Documentation provided to EFSA n. 22). Haematology parameters (RBC count; WBC count; Hb and differential count) were determined prior to the start of the study and 30, 60 and 90 days after the start of the study. At the end of the 90-day period, all animals were sacrificed. Gross and microscopic examination was performed on a limited number of organs and tissues. Special staining techniques were used to determine the presence of PVP (K-90). The growth of the dogs was significantly decreased in the 5 and 10% PVP (K-90) groups compared to controls. Haematological examinations did not reveal any significant difference among the groups. Gross and microscopic examination of H&E stained slides did not show effects related to treatment. The special staining for the presence of PVP (K-90), showed a positive reaction in the mesenteric lymph nodes of 3 dogs in the 10% and 5% group, one dog of the 2% group and a slight positive reaction in one control animal. The Panel considered that effects on body weight were due to the high levels of test compound added to the basal diet which led to a lower intake of macro- and micronutrients, and therefore considered these effects as treatment-related, but not adverse.

Polyvinylpolypyrrolidone (PVPP)

Rats

Sprague Dawley rats (10/sex per group) were fed diets (Altromin R) containing 0, 1, 2.5, 5 or 10% PVPP (Kollidon CE 5050, cross-linked insoluble polyvinylpyrrolidone, purity 95%), at doses equivalent to 0, 1,200, 3,000, 6,000 and 12,000 mg/kg bw per day, respectively, for 28 days (BASF, 1978; Documentation provided to EFSA n. 23). No effect on body weight gain, feed intake, haematology and clinical chemistry parameters was observed. In the treated females, a dose-dependent increase in casts of the urine sediment was reported, but this finding was reversible during the recovery period. Similarly, the discolouration of faeces (whitish) observed in a dose-dependent manner from 1 week of experimental feeding up to the termination was reversible in the recovery period. Gross and microscopy examinations did not reveal any effects related to the treatment with PVPP and no accumulation of the test item or any decomposition products thereof were found in the intestinal mucous membrane or in mesenteric lymph nodes. The authors reported the NOAEL from this study to be 10% PVPP in the diet equivalent to 12,000 mg/kg bw per day, the highest dose tested. However, the Panel was not able to check the individual data due to the poor readability of the electronic documentation provided.

Sprague Dawley rats (5/sex per group; initial body weight of 160–190 g and 128–152 g for males and females, respectively; 5 weeks old) received by gavage 1,500 mg/kg bw per day of PVPP (Crospovidone,

1-vinyl-2-pyrrolidone homopolymer, a cross-linked homopolymer of polyvinylpyrrolidone) for 90 days (The Center of Japan Biological Chemistry, 1985; Documentation provided to EFSA n. 24). The control group received physiological saline (0.9% NaCl) as a vehicle. Clinical appearance, growth, feed intake, ophthalmological examination did not reveal any differences to controls. Scattered differences to the control group were observed in urinalysis, haematology and clinical chemistry examinations. According to the authors, these changes were slight, their values were within the normal ranges and there was no consistency in the direction of the changes between males and females. Therefore, they were considered by the authors of the study as unrelated to treatment with PVPP. Regarding organ weights, a slight increase in the relative weight of the thyroid of the treated males was reported. The Panel noted that the value was reported by the authors as being in the normal range, that the absolute weight of thyroid was reported as comparable to that in the control group, and that there were no corresponding microscopic changes in the thyroid. These findings were considered by the Panel of no toxicological significance. Gross and microscopic examinations did not reveal any effects related to the treatment with PVPP. The Panel considered that the only dose tested of 1,500 mg/kg bw per day did not give rise to any adverse effect.

Three groups of FDRL/Wistar rats (20/sex per group) received in the diet 0 (concurrent control), 2 or 10% of PVPP (equivalent to 1,800 or 9,000 mg PVPP/kg bw per day, respectively) for 90 days (Food and Drug Research Laboratories, Inc 1976; Documentation provided to EFSA n. 25). In addition, a 4th group (20/sex per group) kept on the diet without PVPP added served as a paired feeding control for the high-dose group. Clinical appearance, body weight gain, feed intake and efficiency of feed utilisation, haematology, clinical chemistry and urinalysis parameters, organ weights and gross and microscopic examinations of representative tissues did not reveal any findings related to the treatment. Analysis of organ weights revealed an apparent decrease in relative and absolute prostate weights of PVPP-treated males. The Panel checked the data for relative prostate weights for normal distribution and performed analysis of variance (ANOVA) followed by Student's t-tests for each test group and control. The relative prostate weights were statistically significantly lower in both test groups than the relative prostate weights of the two control groups. According to the authors, based on lack of macroscopic and microscopic changes in the gland and a considerable individual variation in the weight of prostate, this finding was not toxicologically significant. The Panel noted that the mean absolute prostate weight in the low- and high-dose groups were 69% and 61% of the mean control values, that the relative prostate weights were 65% and 62% of the mean control values and that the differences to controls were statistically significant at the two dose levels tested. However, due to large variation in individual data on the prostate weight and the lack of histopathological changes, the authors concluded that the effect on prostate weight was of no toxicological significance. The Panel considered that the lack of other testosterone-related effects such as on the testes supported this conclusion. The authors considered 9,000 mg PVPP/kg bw per day as the NOAEL in this study.

Dogs

Beagle dogs (3/sex per group) received by gavage 1,000, 2,000 or 4,000 mg PVPP (Kollidon CE 5050)/kg bw per day for 28 days (Laboratorium Fur Pharmakologie und Toxikologie, 1973; Documentation provided to EFSA n. 26). One control group received a vehicle (tap water) and another one 4,000 mg cellulose/kg bw per day. Clinical appearance, growth, feed and water intake, haematology, clinical chemistry and urinalysis parameters, ophthalmological examination, electrocardiography, organ weights and gross and microscopic examinations did not reveal any effects related to the treatment with PVPP. The authors considered the NOAEL to be 4,000 mg PVPP/kg bw per day, the highest dose tested. However, the Panel was not able to check the individual data due to the poor readability of the electronic documentation provided.

Beagle dogs, aged 7–8 months, were divided into two groups (3 dogs/sex per group) and given either 0 (controls) or 1,000 mg PVPP (crospovidone, 1-vinyl-2-pyrrolidinone homopolymer)/kg bw per day in gelatine capsules for 90 days (Fuji Life Science Inc., 1985; Documentation provided to EFSA n. 27). The controls were administered gelatine capsules only. During the study, general condition was recorded at least twice per day and body weight and food consumption once per week. Haematology (WBC, RBC, platelet count, Hb, Ht, diff. WBC, clotting time, APTT and erythrocyte sedimentation rate), blood chemistry (GOT, GPT, ALP, LDH, BUN, glucose, triglyceride, total cholesterol, Alb, TP, creatinine, P, Ca, Na, K, Cl), urinalysis (sediment, pH, protein, glucose, ketone bodies, urobilinogen, bilirubin and occult blood) and ophthalmology were recorded prior to the start of the study and at 7 and 13 weeks. At necropsy, the weight of the brain, pituitary, submandibular gland, thyroid, heart, lungs, liver, spleen, kidneys, adrenals, thymus, prostate, testis, epididymides, ovaries and uterus was measured. Apart

from these organs and tissues, the parotid gland, tongue, mammary gland, sternum, femur (with bone marrow), larynx, trachea, parathyroids, oesophagus, stomach, duodenum, jejunum, ileum, colon, rectum, mesenteric lymph nodes, pancreas, urinary bladder, vagina, eyes, skin and spinal cord were collected and subject to microscopical examination. No treatment-related changes were found, except from day 2 onwards white contaminants suggestive of the test compound were found in the faeces of all dogs treated with PVPP. The authors concluded that 1,000 mg PVPP/kg bw per day is the NOAEL, the only dose tested. The Panel agreed with this conclusion.

Groups of four male and four female pure-bred Beagle dogs were daily given PVPP (Kollidon CE 5050) by gavage in doses of 300, 1,200 and 4,800 mg/kg body weight for 6 months (Laboratorium Fur Pharmakologie und Toxikologie, 1978; Documentation provided to EFSA n. 28). The test compound was suspended in 10 ml distilled water/kg bw. Four male and four female control animals received 10 ml of the vehicle/kg bw and four male and four female control animals received 4,800 mg cellulose/kg bw. Behaviour, external appearance, intake of food and drinking water, gain weight, haematological (Hb, Ht, erythrocyte, leucocyte and differential counts, prothrombin time, clotting time, erythrocyte sedimentation rate, platelet and reticulocyte counts), clinical chemistry (glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, glucose, blood urea nitrogen, alkaline phosphatase, total bilirubin, total protein, sodium, potassium, calcium, chloride, uric acid, liver function, albumin, globulin) and electrocardiographic investigations, urinalysis, ophthalmology, circulatory function, hearing and dentition as well as gross observation and organ weights (heart, liver, lungs, spleen, kidneys, adrenals, thymus, pituitary, testes, ovaries, thyroids, brain) at necropsy did not reveal any treatment-related changes of the test compound up to the dose level of 4,800 mg/kg bw per day. No animal died prematurely. Histopathological examination of 34 organs and tissues of all animals did not reveal any change that could be attributed to the treatment with PVPP. The authors considered the highest dose of 4,800 mg PVPP/kg bw per day as the NOAEL. The Panel agreed with this conclusion.

Overall, feeding of rats up to 9,000 mg PVP/kg bw per day in the basal diet for up to 90 days had no adverse effects. Feeding of dogs with PVP up to 2,500 mg/kg bw per day for 90 days showed no adverse effects. No treatment-related effects were seen in rabbits receiving up to 2,700 mg PVP/kg bw per day by gavage for 4 weeks.

PVPP had no adverse effects in rats receiving for 28 days a diet containing up to 12,000 mg PVPP/kg bw per day or given by gavage a dose of 1,500 mg PVPP/kg per day for 90 days. Dietary administration of PVPP to rats for 90 days resulted in an NOAEL of 9,000 mg/kg bw per day. In dogs, no treatment-related adverse effects were seen in 90-day studies in which bolus doses of 1,000 mg PVPP/kg bw per day (capsules) or up to 4,800 mg PVP/kg bw (gavage) were administered for 6 months.

3.6.4. Genotoxicity

Polyvinylpyrrolidone (PVP)

The genotoxicity of polyvinylpyrrolidone (commercial products Povidone K-30, PVP K-30, Kollidon® 30) was first evaluated by JECFA in 1980. The Committee reported what follows:

'*Povidone K-30 was tested for mutagenic effects on the germ cells of male mice (dominant lethal test) after one intraperitoneal application. The animals received a single injection of 3 160 mg povidone K-30 (dissolved in aquadest.) per kg body weight in a volume of 10 ml/kg. No animals displayed any recognisable symptoms of toxicity over the entire test period. The administration of povidone K-30 had no effect on the conception rate, average number of implantations, percentage of living foetuses or the mutagenicity index (BASF 1977e). Mutagenicity and transformation tests in vitro employing mouse cells (lymphoma L5178Y, TK+/-BUDR and Balb/3T3, respectively) demonstrated that PVP at concentrations of 0.5%, 1.0%, 5.0% and 10.0% in the media did not cause significant mutagenic or transformation effects when compared to non-treated cells (Carchman, 1978)*'.

In a subsequent evaluation by the SCF (1992), the SCF concluded that PVP was toxicologically acceptable based on – *inter alia* – the results of *in vitro* mutagenicity studies, not reported in detail in that opinion which cross refered to the previous JECFA (1980) evaluation.

Further genotoxicity studies on PVP (K30) are described in a published review (Robinson et al., 1990). Negative results are reported in the following studies: i) Ames test, at doses up to 5 mg/plate (Clairol Labs, 1978), or 3.5% solution (Bruce, 1977), or 10 mg/plate, with and without metabolic activation (Zeiger et al., 1987); ii) gene mutation in mouse lymphoma L5178Y cells, in the dose range 1–100 mg/ml with and without metabolic activation (Kessler et al., 1980); iii) morphological transformation in Balb/c 3T3 cells, in the dose range 1–100 mg/ml (Kessler et al., 1980); iv) dominant

lethal test in male mice administered once with PVP (K-30) by i.p. at 3.16 mg/kg bw (Zeller and Engelhardt, 1977); v) bone marrow chromosomal aberrations in male and female Chinese hamsters treated once with PVP (K-30) by i.p. at 3.16 mg/kg bw (BASF, 1980).

Only few of the studies quoted above were available to the Panel for evaluation: the Ames test on PVP performed in the framework of the National Toxicology Program, reported by Zeiger et al. (1987), the mouse lymphoma and cell transformation assays published by Kessler et al. (1980) and the summary of the unpublished report of the mouse dominant lethal study, submitted through the public call for data (Zeller and Engelhardt, 1977 in BASF, 1977; Documentation provided to EFSA n. 29). All studies were evaluated as negative by the Panel, although the limitation of the test protocols in force at the time the studies were performed were noted (not for the Zeiger study 1987, which meets current criteria).

Supplementary information for the evaluation of genotoxicity of PVP/PVPP are provided by the QSAR analysis of the polymer and related substances. A structure–activity analysis of PVP, NVP, 2-pyrrolidone and N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone was performed by the OECD QSAR ToolBox (version 3.3), using a series of profilers for DNA reactivity and genotoxicity. No structural alerts for *in vitro* genotoxicity (Ames test, micronuclei and chromosomal aberrations with Oasis v.1.3 and ISS Ames profilers) and DNA binding (Oasis v.1.3) for either PVP, NVP, 2-pyrrolidone and N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone (Appendix E). An alert for possible DNA binding was identified in PVP, NVP and N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone by the OECD DNA-binding profiler; however, the Panel noted that the DNA binding potential flagged by the OECD profiler is generically attributed to aliphatic tertiary amines, assuming the subsequent formation of iminium ion and SN1 reaction, which is not supported by available biological data on NVP. An alert for *in vivo* genotoxicity was identified by another profiler (micronucleus by ISS) in all substances; the Panel noted that the alert for *in vivo* genotoxicity highlighted by the ISS profiler (H-acceptor-path-3-H-acceptor) is related to the potential non-covalent binding with DNA or protein, and it is considered too unspecific to retain predictive value (EFSA ANS Panel, 2017a). Overall, the Panel concluded that the (Q)SAR analysis of PVP, NVP, 2-PY and N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone did not identify reliable alerts for DNA reactivity and genotoxicity in their structures.

In addition to data on PVP/PVPP, also information on the genotoxicity of the following potential impurities of the polymers was considered.

N-vinyl-2-pyrrolidone (NVP)

No new data on NVP were available to the Panel for evaluation. However, the Panel noted that a comprehensive battery of genotoxicity short-term tests, including studies in bacterial systems, chromosomal aberrations and sister chromatid exchanges in human lymphocytes, gene mutations at *tk* and HPRT loci in mouse lymphoma cells, unscheduled DNA synthesis in rat hepatocytes, cell transformation in Balb/c 3T3 cells, sex-linked recessive lethals in *Drosophila* and *in vivo* mouse bone marrow micronucleus assay, had been previously evaluated by the SCF, and that based on the negative results obtained the SCF had concluded that *'NVP does not appear to be genotoxic in vitro or in vivo'* (SCF, 2002).

2-pyrrolidone (2-PY)

No experimental data on genotoxicity of 2-PY were available for evaluation. A single paper, retrieved from the open literature (Mayer et al., 1988) and concerning the induction of aneuploidy in yeast, was considered by the Panel not relevant for human risk assessment.

However, even though no published genotoxicity studies on 2-PY were available, the Panel noted that toxicological information have been provided to the ECHA C&L Inventory by a number (483) of companies from 18 notifications, and that no specific labelling for genotoxicity was proposed.

N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone

N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone, an impurity and by-product of PVP manufacturing process (Section 3.1.3) was tested in the Salmonella/microsome assay with strains TA1535, TA1537, TA98 and TA100 at 20, 100, 500, 2,500 and 5,000 μg/plate. Repeated experiments were performed using the standard plate incorporation procedure. The results were negative (BASF, 1985; Documentation provided to EFSA n. 30).

N,N'-Divinyl-imidazolidone

Information on genetic toxicology of N,N'-divinyl-imidazolidone is available from the ECHA database (https://echa.europa.eu/registration-dossier/-/registered-dossier/16731/7/7/1). In *in vitro* studies, the test substance was not mutagenic in the Ames test (doses from 20 to 5,000 ug/plate, with and without metabolic activation in four Salmonella Typhimurium strains) and in a gene mutation assay at the HPRT locus in mammalian cells, while it induced structural chromosome aberrations (no details given for these studies). In addition to the *in vitro* studies, also an *in vivo* study was available and independently evaluated. *In vivo* N,N'-divinyl-imidazolidone was tested in micronucleus assay in mouse bone marrow, with i.p. administration up the maximum tolerated dose (300 mg/kg bw). No induction of micronucleated polychromatic erythrocytes was observed; high dose treatment elicited a significant inhibition of erythropoiesis, demonstrating the exposure of bone marrow to the test substance. Negative results in an *in vivo* UDS assay are also mentioned with no further details. Overall, the available information on N,N'-divinyl-imidazolidone does not raise concern for *in vivo* genotoxicity.

Triethanolamine formate

Triethanolamine formate is an ester of formic acid and triethanolamine, and it is expected to be hydrolysed to its constituents.

Information on the genetic toxicology of formic acid is available from the ECHA database (https://echa.europa.eu/it/information-on-chemicals/cl-inventory-database/-/discli/details/33315). Formic acid was not genotoxic in valid in vitro assays for gene mutation using bacteria (TA97, TA98, TA100, and TA1535) and mammalian cells (HPRT), with and without metabolic activation, and it was negative in cytogenetic assays in vitro as it did not induce Chromosome Aberration or Sister Chromatid Exchange in mammalian cells. Formic acid was negative in the Sex-linked Recessive Lethal Test in Drosophila melanogaster in vivo.

The genetic toxicity of triethanolamine was extensively evaluated in the context of an NTP Toxicology and Carcinogenicity study (NTP, 2004). Triethanolamine was not mutagenic in any of the *in vitro* or *in vivo* tests performed. It did not induce mutations in S. Typhimurium, sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with and without metabolic activation. Triethanolamine did not induce sex-linked recessive lethal mutations in germ cells of adult male Drosophila melanogaster exposed by feeding or injection. No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples of male or female mice that received dermal applications of triethanolamine for 13 weeks.

Overall, the available data indicate that triethanolamine formate does not raise concern for genotoxicity.

N-Nitroso-2-pyrrolidinone (N-Nitroso-2-PY)

Lactams such as 2-pyrrolidone can easily undergo nitrosation (Torra et al., 1989). When 2-pyrrolidone was treated with excess nitrite under acidic conditions, it was converted to a large extent (> 50%) into N-nitrosopyrrolidone (Mende et al., 1994). According to the authors of the study, data support the possible conversion of 2-PY to N-nitroso-2-PY in the acidic gastric environment.

N-nitroso-2-PY tested positive in an early study using a Bacillus subtilis DNA repair deficient strain (H17 vs. M45) (Leifer et al., 1981), and it is anticipated to be reactive to DNA and genotoxic by QSAR analysis (Appendix E). Therefore, a characterisation of the risk posed by the endogenous formation of N-nitroso-2-PY following ingestion of 2-PY present as impurity in PVP used as food additive was performed. To this aim, the same approach used for the evaluation of the endogenous formation of nitrosamines following the use of nitrates and nitrites as food additives was applied (EFSA ANS Panel, 2017b).

The daily dose of N-nitroso-2-PY formed was estimated based on the following empirical equation, derived from the Canadian Drinking Water Guidelines (further details in EFSA ANS Panel, 2017b):

$$DD_{nitros} = ([NO_2]^2 \times DI_{DMA} \times K_{am} \times 3,600 \times MW_{nitros})/\text{body weight}.$$

In which where DD_{nitros} is the daily dose of the nitrosamine (mg/kg bw per day); $[NO_2]$ is the concentration of NO_2 in the stomach of 2.1×10^{-4}mol/L per day (at the ADI of NO_2^- as food additive); DI_{DMA} is the estimated daily intake of the precursor secondary amine (2-PY) in moles per day; K_{am} is the nitrosability rate constant of 0.002 $((mol/L)^{-2}s^{-1})$; 3,600 is an estimation of the time during which the concentrations of the nitrosable precursor (2PY) and nitrite precursors would remain

constant through the oesophageal/cardia region, measured in sec; MW is molecular weight of N-nitroso-2-PY in mg/mol (130×10^3), and the body weight 70 kg.

Assuming as worst case the daily exposure to 21 mg PVP/kg bw in adults (Section 3.4), and a content of 3.0% 2-PY as an impurity (Section 3.1.2), the resulting daily intake of 2-PY due to the use of PVP as food additive would be 0.63 mg × 70 kg bw, i.e. 44.1 mg or 0.5×10^{-3} moles/day. Based on the above equation, the daily dose of N-nitroso-2-PY would be:

$$[(2.1 \times 10^{-4})^2 \times 0.5 \times 10^{-3} \times 0.002 \times 3{,}600 \times 130 \times 10^3]/70 = 0.3 \times 10^{-6} \text{ mg/kg bw per day.}$$

As no carcinogenicity data on N-nitroso-2-PY are available, the size of MoE can tentatively be evaluated considering the $BMDL_{10}$ of the structurally related carcinogen N-nitrosopyrrolidine (0.16 mg/kg bw per day; SCCS, 2012). The resulting MoE will be 0.16: $0.3 \times 10^{-6} = 5 \times 10^5$, which indicates a very low safety concern (EFSA, 2005).

Overall, based on the results of the available *in vitro* and *in vivo* studies on PVP and its precursor N-vinyl-2-pyrrolidone (NVP), and information on genotoxicity of the potential impurities 2-pyrrolidone (2-PY), N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone, N,N′-divinyl-imidazolidone and triethanolamine formate, the Panel concluded that PVP used as a food additive does not raise a concern with respect to genotoxicity. The Panel considered that this conclusion would also apply to PVPP. The Panel also noted that even under the scenario of 3% content of 2-PY in PVP, the risk related to endogenous nitrosation of 2-PY is very low.

3.6.5. Chronic toxicity and carcinogenicity

Polyvinylpyrrolidone (PVP)

Rats

A chronic oral toxicity study with PVP (K-30; 'General Aniline and Film Corporation PVP') in rats was submitted by the interested party (Industrial Biology Research and Testing Laboratories, 1957; Documentation provided to EFSA n. 31).

The interim study report after 12 months is not available. Therefore, the Panel did not have the study design available. The strain of rats used as well as the number of animals per sex per group is not given.

The albino rats were given 0% (controls), 1% or 10% PVP by weight in their diet (equivalent to 500 or 5,000 mg/kg bw per day) for 24 months. Body weight was recorded every month during the second year of the study. Haematology was performed on all groups (number of animals per group not given) at the end of the 15, 18, 21 and 24 months. Urinalysis (pH, sugar, albumin content and density) consisted of pooled urine of five animals of each group (it is not clear whether males and females were studied separately) at the end of 15, 18, 21 and 24 months. Two animals of each dosage group (one male and one female) and from the controls were necropsied at the end of 18 months. Ten animals from each dosage groups and 10 from the controls (five males and five females per group) were necropsied after 24 months. The weight of the brain, lung, heart, liver, stomach, kidneys, spleen, ovaries + uterus was determined. Histopathology was performed on stomach, skin, intestine, pancreas, liver, heart, spleen, lung, kidneys, brain and ovary or testes. All animals that died during the course of the study were necropsied and examined grossly for cause of death.

Animals of the 10% PVP group gained less weight, but the difference with the controls was less than 10%. Haematology, urinalysis and gross and histopathology did not demonstrate any adverse effect that could be attributed to the PVP diet. The authors concluded that the NOAEL of this chronic study is 10% PVP (equivalent to 5,000 mg/kg bw per day) in the diet. The Panel considered the design of the study to be too limited (e.g. number of animals per sex per group, number or organs and tissues evaluated) to be used for risk assessment.

A total of 450 Sprague Dawley rats were treated with PVP (Kollidon 90) in the diet at 1%, 2.5% or 5% (equivalent to 500, 1,250 or 2,500 mg/kg bw per day, respectively) for 129 (males) or 138 weeks (females) and compared with 250 control rats (BASF, 1980; Documentation provided to EFSA n. 32). The control rats (125 males and 125 females) received 5% cellulose in the feed. Ten rats (five of each sex) were necropsied after 26, 52 and 104 weeks or after 39, 65 or 117 weeks (26, 52 or 104 weeks of exposure followed by a 13-week recovery period). Final necropsy was scheduled after 129 weeks (45 males of the treatment groups and 95 control males) or 138 weeks (45 females of the treatment groups and 95 control females). Behaviour, external appearance and food and drinking water consumption were observed daily. Food intake was determined at 4-week intervals. Haematological

examinations, leucocyte counts and differential counts were determined in all surviving males in test week 129 and in all surviving females in week 138 and as far as possible also in prematurely necropsied animals. Immediately before dissection, the rats were examined ophthalmologically. The auditory function was checked by a simple noise test. Animals which died or were found moribund and killed prematurely were dissected and inspected grossly. The weights of 11 organs (heart, liver, lungs, spleen, kidneys, adrenal, thymus, pituitary, gonads, thyroids, brain) were determined. Surviving rats were necropsied and histopathological examinations (which comprised non-, hyperplastic and neoplastic lesions) were made of 30 organs and tissues and of tumours and areas in which tumours were suspected. Further, to detect signs of storage, special stains (Sudan black, Giemsa and PAS) were made in heart, liver, kidneys and mesenteric lymph nodes.

Mortality was in the normal range and the cause of death was largely similar between treated and control animals. All results observed at the interim necropsies were within the normal range and nothing unusual was observed during the follow-up periods. Behaviour, clinical observations, faeces, intake of food and drinking water, body weight gain, leucocyte and differential count, examination of sight, hearing and detention, organ weights and gross and microscopic examination did not indicate any treatment-related effects of PVP. No accumulation of the test compound in heart, liver, kidneys or mesenteric lymph nodes was found. The NOAEL of this chronic toxicity/carcinogenicity study is considered to be 5% PVP in the feed (equivalent to 2,500 mg/kg bw per day), the highest dose tested.

PVP (K-25, Kollidon 25) was administered to Sprague Dawley rats (50 rats/sex per group) for 2 years in concentrations of 50,000 or 100,000 mg/kg diet (equivalent to 2,500 or 5,000 mg/kg bw per day). An untreated group (0 mg/kg diet) and a group receiving 50,000 mg cellulose/kg diet were included as controls (BASF, 1978; Documentation provided to EFSA n. 33). PVP appeared tolerable in both doses. Food intake and body weight gain were similar among the groups. After 2, 4, 10 and 16 months and prior to the final necropsy, blood was collected from 10 males and 10 females of each group and analysed for Hb, erythrocytes, Ht, leucocytes, differential blood count, urea and GPT. Urine was examined, at the same intervals as the blood samples, from 10 males and 10 females for pH, albumin, glucose, urobilinogen and sediment. At necropsy, in addition to body weight, the weight of the heart, liver and kidneys was determined. Microscopic examination was performed on a brain, heart, lung, thyroid, liver, stomach, mesenteric lymph nodes, small and large intestines, spleen, kidneys, adrenals, pancreas, urinary bladder, testes, ovaries and all tumours. Haematology, clinical chemistry, urinalysis, absolute and relative organ weights did not show any abnormality that could be related to the treatment with PVP 25. Histopathological examination of animals that died or were killed intercurrently did not exhibit any abnormality related to the administration of the test compound. Survival was similar among the groups. With respect to the incidence of benign and malignant tumours in the treated groups, this was not significantly different from the controls. Neither in the intestinal mucosa nor in the mesenteric lymph nodes, there was any indication of accumulation of PVP 25. The Panel considered 5,000 mg/kg bw per day the NOAEL, the highest dose tested, but noted the limited number of organs and tissues histopathologically examined.

Three groups of 100 rats of the Sherman Wistar strain containing 50 males and 50 females were exposed to PVP (Plasdone, PVP K-30) via the diet for 2 years as follows: group 1, 1% PVP (equivalent to 500 mg/kg bw per day); group 2, 10% PVP (equivalent to 5,000 mg/kg bw per day); group 3, controls (Industrial Biology Res. Testing Labs for Antara Chemicals, year not given; Documentation provided to EFSA n. 34). Each month the animals were weighted. Complete haematology (no details available) was performed at 3-month intervals). Urinalysis (pH, sugar, albumin content and density) was determined each 3 months from pooled urine of five animals. Ten animals of each group were necropsied after 24 months and grossly examined. Histopathology was conducted on stomach, skin, intestine, pancreas, liver, heart, spleen, lung, kidney, brain, testes and ovaries. All animals that died during the study were examined grossly for cause of death. The addition of 10% of PVP by weight in the diet for a period of 24 months did not cause any adverse effect, except a slight effect (less than 10% difference) on the weight gain. There was no significant pathology observed, either during gross or microscopic examination, which could be attributed to exposure to the test compound. The authors concluded that 10% PVP in the diet (equivalent to 5,000 mg/kg bw per day) is the NOAEL. The Panel noted that the present study was only available as a summary; no further details of the results were available.

Dogs

Groups of two male and two female Beagle dogs were exposed via the diet to 10% cellulose (Solka Floc; control group); 2% PVP (Plasdone, PVP K-30) + 8% cellulose; 5% PVP + 5% cellulose or 10%

PVP for 2 years. During the study analyses of food consumption, weight gain, blood and urine (details not given) and gross behaviour and appearance were recorded (Antara Chemicals, 1957; Documentation provided to EFSA n. 35). Microscopy was performed on samples of the thyroid, parathyroid, heart, lung, rib bone and bone marrow, skin, small intestines, large intestines, liver, gall bladder, spleen, kidneys, lymph nodes, urinary bladder, uterus or prostate, left adrenal, pancreas and testis or ovary. At the end of the 2-year study, all animals were in good health. Growth was in the normal range and periodic blood and urine analyses showed values in the normal range (no data available). Gross and microscopic pathology were conducted at the end of the experimental period. Organ weights and gross observations were normal (no details given). Microscopic examination was essentially negative except for the presence of swollen reticuloendothelial cells in the lymph nodes of the 10% PVP group. In the 2 and 5% groups, a similar histopathological change was observed but less consistent and to a lesser degree. This effect was considered reversible and a transient effect, possible related to the elimination of PVP. Based on these observations, the authors considered the highest dose of 10% (equivalent to 2,500 mg/kg bw per day) PVP as the NOAEL. The Panel noted that the design was limited (low number of dogs per group). Only a summary of this study was available and details were not given.

Overall, chronic studies with 5,000 mg PVP (K-25 or K-30)/kg bw per day in rats or 2,500 mg PVP (K-30)/kg bw per day in dogs, both the highest dose tested, showed no toxicity or carcinogenicity. However, the Panel noted that these studies were limited in design and reporting. A well-conducted 2-year oral study in Sprague Dawley rats demonstrated that exposure to 2,500 mg PVP (K-90), the highest dose tested, is neither toxic nor carcinogenic. No chronic toxicity or carcinogenicity studies with PVPP were available.

Polyvinylpolypyrrolidone (PVPP)

No chronic toxicity or carcinogenicity studies were available.

3.6.6. Reproductive and developmental toxicity

Polyvinylpyrrolidone (PVP)

Reproductive toxicity

No reproductive studies were available.

Developmental toxicity

A prenatal developmental toxicity study was performed in Sprague Dawley rats. PVP (Kollidon 25) was administered via the diet to pregnant female rats (n = 26/group) at a concentration of 0 or 100,000 mg/kg diet (equivalent to 0 or 5,000 mg/kg bw per day) from gestation day (GD) 0–20 (BASF, 1975; Documentation provided to EFSA n. 36). During the study mortality, clinical signs, body weight and food intake were measured at regular intervals. A Caesarean section was performed on GD 20, the number of corpora lutea, implantations, resorptions, live and dead fetuses, placental and fetal weight and length were recorded. Two-thirds of the fetuses of each litter were observed for skeletal abnormalities and the other one-third for visceral abnormalities. No overt signs of toxicity were observed in the dams apart from soft stool. The dams showed a decreased body weight gain during the first 6 days of administration of the test substance which was related to decreased food intake during this period. No other effects on the dams or development of the fetuses was observed.

A prenatal developmental toxicity study was performed in Sprague Dawley rats. PVP (Kollidon 90) was administered via the diet to pregnant female rats (n = 26/group) at a concentration of 0 or 100,000 mg/kg diet (equivalent to 0 or 5,000 mg/kg bw per day) from gestation day (GD) 0–20 (BASF, 1975; Documentation provided to EFSA n. 37). During the study mortality, clinical signs, body weight and food intake were measured at regular intervals. A Caesarean section was performed on GD 20, the number of corpora lutea, implantations, resorptions, live and dead fetuses, placental and fetal weight and length were recorded. Two-thirds of the fetuses of each litter were observed for skeletal abnormalities and the other one-third for visceral abnormalities. No overt signs of toxicity were observed in the dams. The dams showed a decreased body weight gain during gestation which was not related to a lower feed intake. The Panel noted that the energy contents of the feed in the highest dose group were 10% less than that of the control group. No other effects on the dams or development of the fetuses was observed.

Polyvinylpolypyrrolidone (PVPP)

Reproductive toxicity

No reproductive studies were available.

Developmental toxicity

A prenatal developmental toxicity study by gavage with PVPP (Kolllidon CE 5050) was performed in Sprague Dawley rats (n = 26) (BASF, 1977; Documentation provided to EFSA n. 38). PVPP was suspended in 0.5% carboxymethyl cellulose and administered at doses of 0, 1,000 and 3,000 mg/kg bw per day from GD 6-15. The concentration of the suspensions was adjusted so as to contain 10 (mid-dose) or 30 mL (high-dose) substance per kg body weight. Control animals received 30 ml/kg of 0.5% CMC preparation. Test substance suspensions were prepared fresh daily. During the study mortality, clinical signs, body weight and food intake were measured at regular intervals. A Caesarean section was performed on GD 20, the number of corpora lutea, implantations, resorptions, live and dead fetuses, placental and fetal weight and length was recorded. Two-thirds of the fetuses of each litter were observed for skeletal abnormalities and the other one-third for visceral abnormalities. No overt signs of toxicity were observed in the dams apart from light stool from day 3 of treatment. The body weight change of the dams receiving 3,000 mg PVPP was lower from GD 0-11. Male and female fetuses of the high-dose group were heavier than fetuses from the control group. No other maternal or developmental effects were observed. The authors considered the high dose (3,000 mg/kg bw per day) as the NOAEL and the Panel agreed with this conclusion.

A peri- and postnatal toxicity study by gavage with PVPP (Kolllidon CE 5050) was performed in Sprague Dawley rats (n = 12) (BASF, 1977; Documentation provided to EFSA n. 38). PVPP was suspended in 0.5% carboxymethyl cellulose and administered at doses of 0, 1,000 and 3,000 mg/kg bw per day from GD 15 to postnatal day 21. Dams were allowed to litter. During the study mortality, clinical signs, body weight and food intake were measured at regular intervals. The behaviour of animals during delivery, litter size, weight and development of the pups, behaviour of the pups and clinical symptoms, pup mortality rate and survival ability were evaluated. No effects on mortality were observed. Lighter stool was observed from day 2–3 of treatment in dams of the high-dose group. The body weight of the dams of the high-dose group was increased on day 21 post-partum. At necropsy, a statistically significant higher absolute and relative spleen weight was observed in the dams of the mid- and high-dose groups when compared with the dams dosed with carboxymethyl cellulose (0.49, 0.52 vs. 0.46 g). The pups of one dam of the high-dose group displayed sparse hair growth and those from another dam of this group had diarrhoea with bloody contents. The pup organ weights and organ: body weight ratios of the pups were in some cases increased and in other cases reduced, but there was no evidence of change due to administration of substance. The interested party considered the high dose (3,000 mg/kg bw per day) as the NOAEL, and the Panel agreed that the highest dose was the NOAEL for developmental toxicity. Based on the effect on spleen weight, the Panel considered 1,000 mg/kg bw per day as a lowest observed adverse effect level (LOAEL) for maternal toxicity. However, no effects on spleen weight, histology or other related effects were observed in the subchronic studies in rats or in the F1 pups of this study.

In summary, no reproductive toxicity studies were available for PVP and PVPP. No adverse developmental effects of PVP were observed in two prenatal developmental toxicity studies at the highest dose tested (5,000 mg/kg bw per day) after administration from GD 0-20. No adverse developmental effects were observed in the prenatal developmental toxicity study after administration of PVPP from GD 6–15 at the highest dose tested (3,000 mg/kg bw per day), and in a peri- and postnatal study after administration from GD 15 to postnatal day 21 at the highest dose tested (3,000 mg/kg bw per day).

3.6.7. Hypersensitivity and immunotoxicity

Both polyvinylpyrrolidone (Gorskaya et al., 2012) and PVPP (Whithmore et al., 2004) are T-cell independent antigens, but no adverse immunologic effects after ingestion of either molecule have been reported.

3.7. Discussion

Polyvinylpyrrolidone and polyvinylypolypyrrolidone, commonly identified with the respective acronyms PVP and PVPP, are authorised as food additives in the EU, respectively, E 1201 and E 1202,

in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

PVP and PVPP are homopolymers of the N-vinyl-2-pyrrolidone monomer. While PVP exhibits a linear polymeric structure, PVPP is cross-linked: the same CAS number (9003-39-8) is used to identify both polymers (Documentation provided to EFSA n. 6. PVPP (E 1202) is produced by a polymerisation process that produces cross-linked insoluble polyvinylpyrrolidone. The infrared spectra of soluble polyvinylpyrrolidone (PVP) and insoluble polyvinylpyrrolidone (PVPP) do not reveal any differences (Documentation provided to EFSA n. 3, 6; Haaf, 1985; Bühler, 2008). PVP (E 1201) occurs as a white or nearly white hygroscopic powder, soluble in water, ethanol and other polar organic solvents, and with weight average molecular weight not lower than 25,000 g/mol. PVPP (E 1202) is a white hygroscopic powder, insoluble in water, ethanol and ether. A main difference between both polymers is the solubility in water. According to information provided by the interested party (Documentation provided to EFSA n. 1), PVP polymers are identified based on the weight average molecular weights derived from kinematic viscosity measurements (K-values). PVP grade K-25 or higher (Table 1) are compliant with the EU specification for E 1201 in respect to the minimum weight average molecular weight required.

Soluble PVP polymers are obtained by free-radical polymerisation of N-vinyl-2-pyrrolidone (NVP) in high purity water (Documentation provided to EFSA n. 6, 3). Insoluble polyvinylpyrrolidone (PVPP) can be produced by the polymerisation of N-vinyl-2-pyrrolidone in the presence of either caustic catalyst or N, N'-divinyl-imidazolidone.

According to the interested party (Documentation provided to EFSA n. 2) all PVP and PVPP products are known to form peroxides over time upon prolonged exposure to heat and oxygen. The information provided on the stability of different batches of PVP and PVPP for 24 months at room temperature (Documentation provided to EFSA n. 3), revealed that the levels of peroxides in some samples were above the limit of 400 mg H_2O_2/kg of the European Pharmacopeia (2017).

According to the information provided by interested parties on particle size distribution of PVP and PVPP, the Panel could not exclude the presence of nanosized particles in the analysed materials.

The studies with radiolabelled PVP or PVPP in laboratory rats showed that the vast majority of the dose was found in the faeces with low amount in urine and bile and trace amounts of the radiolabel were detected in the organs. These observations indicated low absorption. The amount that was absorbed was mainly eliminated via the kidney.

Feeding of rats up to 9,000 mg PVP/kg bw per day in the basal diet for up to 90 days had no adverse effects. Feeding of dogs with PVP up to 2,500 mg/kg bw per day for 90 days showed no adverse effects. No treatment-related effects were seen in rabbits receiving up to 2,700 mg PVP/kg bw per day by gavage for 4 weeks.

PVPP had no adverse effects in rats receiving for 28 days a diet with containing up to 12,000 mg PVPP/kg bw per day or given by gavage a dose of 1,500 mg PVPP/kg per day for 90 days. Dietary administration of PVPP to rats for 90 days resulted in an NOAEL of 9,000 mg/kg bw per day. In dogs, no treatment-related adverse effects were seen in 90-day studies in which bolus doses of 1,000 mg PVPP/kg bw per day (capsules) or up to 4,800 mg PVP/kg bw (gavage) were administered for 6 months.

Based on the results of the available *in vitro* and *in vivo* studies on PVP and its precursor N-vinyl-2-pyrrolidone (NVP), and information on genotoxicity of the potential impurities 2-pyrrolidone (2-PY), N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone, N,N'-divinyl-imidazolidone and triethanolamine formate, the Panel concluded that PVP used as a food additive does not raise a concern with respect to genotoxicity. The Panel considered that this conclusion would also apply to PVPP. The Panel also noted that even under the scenario of 3% content of 2-PY in PVPP, the risk related to endogenous nitrosation of 2-PY is very low.

Chronic studies with 5,000 mg PVP (K-25 or K-30)/kg bw per day in rats or 2,500 mg PVP (K-30)/kg bw per day in dogs, both the highest dose tested, showed no toxicity or carcinogenicity. However, the Panel noted that these studies were limited in design and reporting. A well-conducted 2-year oral study in Sprague Dawley rats demonstrated that exposure to 2,500 mg PVP (K-90), the highest dose tested, is neither toxic nor carcinogenic. No chronic toxicity or carcinogenicity studies with PVPP were available.

No reproductive toxicity studies were available for PVP and PVPP; however, no effects on reproductive organs were observed in subchronic and chronic studies. No adverse developmental effects of PVP were observed in two prenatal developmental toxicity studies at the highest dose tested (5,000 mg/kg bw per day) after administration from GD 0-20. No adverse developmental effects were

observed in the prenatal developmental toxicity study after administration of PVPP from GD 6-15 at the highest dose tested (3,000 mg/kg bw per day), and in a peri- and postnatal study after administration from GD 15 to postnatal day 21 at the highest dose tested (3,000 PVPP mg/kg bw per day).

Overall, the Panel considered that sufficient toxicity studies were available for PVP showing no adverse effects at the highest doses tested.

Based on the chemical similarity between PVP and PVPP, and the lack of adverse effects in the available repeated dose toxicity studies, the Panel considered that chronic toxicity data for PVPP are not necessary for the safety assessment of PVPP.

To assess the dietary exposure to PVP (E 1201) and PVPP (E 1202) from their use as food additives according to Annex II to Regulation (EC) No 1333/2008, the exposure to each of the additives was calculated based on the reported use levels. As both food additives are authorised in two food categories at QS and use levels were reported only for food supplements (FC 17.1), the food supplements consumers only scenario was used.

Mean exposure to PVP (E 1201) from its use as a food additive in food supplements ranged from 0.6 mg/kg bw per day in adults to 17.6 mg/kg bw per day in children. The 95th percentile of exposure to PVP (E 1201) ranged from 3.1 mg/kg bw per day in adolescents to 23.7 mg/kg bw per day in children.

For PVPP (E 1202), mean exposure ranged from 0.6 mg/kg bw per day in adults to 18.6 mg/kg bw per day in children. The 95th percentile of exposure to PVPP (E 1202) ranged from 3.3 mg/kg bw per day in adolescents to 25 mg/kg bw per day in children.

The Panel considered overall that the uncertainties identified resulted in an overestimation of the exposure to PVP (E 1201) and PVPP (E 1202) from their use as food additives according to Annex II in food supplements (FC 17.1). The Panel noted that food categories which may contain the additives due to carry-over (Annex III, Part 1, to Regulation (EC) No 1333/2008) were not considered in the current exposure assessment. This could result in an underestimation of the exposure. Data from the Mintel Database indicate that PVP or PVPP is not used in table-top sweeteners; therefore, leaving this food category 11.4.3 out of the exposure assessment is not anticipated to result in a major underestimation of exposure. The presence of PVPP in must, wine and wine products, and beers due to its use as a processing aid is assumed to be negligible owing to the employed filtration step during the production processes of these beverages.

Exposure to PVP (E 1201) resulting from the proposed extension of use of in foods for special medical purposes in tablet and coated tablet form (FC 13.2) was estimated based on an average daily consumption of two tablets, as recommended by the applicants, and a PVP level of 50 mg/tablet. The exposure for consumers of foods for special medical purposes (FC 13.2) would be therefore 100 mg per day, i.e. for adults, 1.4 mg/kg bw per day, for adolescents, 1.9 mg/kg bw per day and for children, 4.3 mg/kg bw per day.

According to the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA ANS Panel, 2014), the Panel considered that there is no need to allocate numerical ADIs for PVP (E 1201) and PVPP (E 1202).

4. Conclusions

According to the conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010 (EFSA ANS Panel, 2014) and given that:

- the exposure assessment carried out by the Panel was based on the reported use and use levels (one food category out of the two food categories in which PVP and PVPP are authorised);
- the 95th percentile of exposure to PVP and PVPP of maximally 23.7 and 25 mg/kg bw per day in children, respectively, was overestimated, because it was assumed that 100% of the food supplements consumed contained PVP or PVPP at the maximum reported use levels;
- extension of use of PVP (E 1201) to foods for special medical purposes (FC 13.2) would result in an exposure of PVP of 4.3 mg/kg bw per day for children;
- the absorption of PVP and PVPP is very low;
- sufficient toxicity data were available for PVP;
- there is no concern with respect to the genotoxicity of PVP and PVPP;
- no carcinogenic effects were reported in carcinogenicity studies in rats at a dose of 2,500 mg PVP/kg bw per day, the highest dose tested;

- there is no need for chronic toxicity/carcinogenicity data for PVPP for the safety assessment of PVPP given the chemical similarity between PVP and PVPP, and the lack of adverse effects in the available repeated dose toxicity studies;

the Panel concluded that there is no need for numerical ADIs for PVP and PVPP, and that there is no safety concern for the reported uses and use levels of PVP and PVPP as food additives. The Panel further concluded that the proposed extension of use is not expected to be of safety concern at the proposed MPL and recommended consumption level.

5. Recommendations

The Panel recommend that the European Commission considers:

- revising of the EU specifications for PVP (E 1201) and PVPP (1202) in order to include better definitions and assays in line with the definitions;
- lowering the current limits for lead in the EU specifications for PVP (E 1201) and PVPP (E 1202) in order to ensure that both food additives will not be a significant source of exposure to lead in food.
- including in the EU specifications for PVP and PVPP, limits for several elements of toxicological importance analysed by the interested parties such as arsenic, cadmium, mercury, chromium, cobalt, copper and nickel;
- change the name of E1202 to 'crosslinked polyvinylpyrrolidone' (synonyms: Crospovidone, Crospovidonum, insoluble polyvinylpyrrolidone, cross-linked PVP, PVPP);
- replacing the term 'molecular weight (average)' by the term 'weight-average molecular weight' for PVP (E 1201) in the EU specifications;
- including a limit for 2-pyrrolidone in the EU specifications for PVP (E1201) and PVPP (E1202);
- revising the range for nitrogen content for PVP and PVPP in the EU specifications;
- including limits for the peroxide content, formic acid and triethanolamine formate in the EU specifications for PVP (E 1201), and for peroxide content in the EU specifications for PVPP (E 1202);
- requesting appropriate data on the potential presence of nanoparticles in PVP (E 1201) and PVPP (1202). The data should be generated in accordance with the EFSA Guidance (2018) and following the principle outlined in the latest Guidance (add the link of the latest one for PC), prior to consideration on the need for inclusion of particle size distribution as an additional parameter in the EU specifications.

Documentation provided to EFSA

1) Ashland Specialities, September 2019. Communication: Reply to the letter "Additional information request on polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202)".
2) Ashland Specialities, April 2020. Communication: Reply to the letter "Additional information request on polyvinylpyrrolidone (E 1201) and polyvinylpolypyrrolidone (E 1202)".
3) Ashland Specialities, November 2017. Reply to the call for technical and toxicological data on miscellaneous food additives to be re-evaluated under the Regulation (EU) No 257/2010 (2017). Technical data on PVP (E 1201) and PVPP (E 1202): sections 1.1–1.4.
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5) Ashland Specialities, November 2017. Reply to the call for technical and toxicological data on miscellaneous food additives to be re-evaluated under the Regulation (EU) No 257/2010 (2017). Toxicological data on PVP (E 1201) and PVPP (E 1202).
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Abbreviations

ADI	Acceptable Daily Intake
bw	Body Weight
CAS	Chemical Abstract Service
ECHA	European Chemicals Agency
EINECS	European Inventory of Existing Commercial chemical Substances
F1	First-generation pups
FAF	Food Additives and Flavourings
FSMP	Food for Special Medical Purposes
GD	Gestation Days
GNPD	Global New Products Database
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD50	Lethal dose, 50% i.e. dose that causes death among 50% of treated animals
LLOQ	Lower limit of quantification
LOAEL	Lowest observed adverse effect level
NOAEL	No observable adverse effect Level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
RBC	Red blood cells
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
RES	reticuloendothelial system
SCF	Scientific Committee for Food
SEM	scanning electron microscopy
TemaNord	Nordic Council of Ministers
TLC	Thin layer chromatography
WBC	White blood cells
WHO	World Health Organization

Appendix A.1 – Summary of reported use levels (mg/kg or mg/L as appropriate) of PVP (E 1201) provided by industry

Appendix A.2 – Summary of reported use levels (mg/kg or mg/L as appropriate) of PVPP (E 1202) provided by industry

Appendix B.1 – Number and percentage of food products labelled with PVP (E 1201) out of the total number of food products present in the Mintel GNPD per food subcategory between 2015 and 2020

Appendix B.2 – Number and percentage of food products labelled with PVPP (E 1202) out of the total number of food products present in the Mintel GNPD per food subcategory between 2015 and 2020

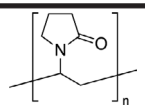
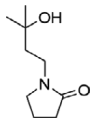
Appendix C – Concentration levels used in the exposure assessment scenarios (mg/kg or mL/kg as appropriate)

Appendix D.1 – Summary of total estimated exposure of PVP (E 1201) from its use as a food additive for the food supplements consumers only scenario per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix D.2 – Summary of total estimated exposure of PVPP (E 1202) from its use as a food additive for the food supplements consumers only scenario per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendices A–D can be found in the online version of this output ('Supporting information' section) https://doi.org/10.2903/j.efsa.2020.6215

Appendix E – Structural alerts for genotoxicity in polyvinylpyrrolidone and related compounds (QSAR ToolBox 3.3)

	Chemical #1	Chemical #2	Chemical #3	Chemical #4	Chemical #5
Substance identity					
Structure					
CAS number	9003-39-8	616-45-5	88-12-0	No CAS number	54634-49-0
Chemical name	Polyvinylpyrrolidone	2-pyrrolidone	N-vinyl-2-pyrrolidone	N-(3′-hydroxy-3′-methylbutyl) -2-pyrrolidone	N-nitroso-2-pyrrolidone
Profilers					
General Mechanistic					
DNA binding by OASIS	No alert found	No alert found	No alert found	No alert found	SN1 >> nucleophilic attack after metabolic conversion
DNA binding by OECD	SN1 >> iminium ion formation	No alert found	SN1 >> iminium ion formation	SN1 >> iminium ion formation	SN1 >> carbenium ion formation
Carcinogenicity (genotox and non-genotox) by ISS	No alert found	No alert found	No alert found	No alert found	Alkyl and aryl N-nitroso group – structural alert for genotoxic carcinogenicity
Endpoint Specific					
In vitro mutagenicity (Ames test) alerts by ISS	No alert found	No alert found	No alert found	No alert found	Alkyl and aryl N-nitroso group
DNA alerts for CA and MNT by OASIS	No alert found	No alert found	No alert found	No alert found	SN1 >> nucleophilic attack after metabolic conversion
In vivo mutagenicity (Micronucleus) alerts by ISS	H-acceptor-path-3-H-acceptor	H-acceptor-path-3-H-acceptor	H-acceptor-path-3-H-acceptor	H-acceptor-path-3-H-acceptor	Alkyl and aryl N-nitroso group and H-acceptor-path-3-H-acceptor
DNA alerts for AMES by OASIS	No alert found	No alert found	No alert found	No alert found	SN1 >> nucleophilic attack after metabolic conversion
Protein binding alerts for Chromosomal aberration by OASIS	No alert found	No alert found	No alert found	No alert found	No alert found