

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	Basic Methacrylate Copolymer
Question(s) to be answered by JECFA <i>(Provide a brief justification of the request in case of re-evaluations)</i>	Safety evaluation and establishment of specification when used as glazing / coating agent.

1. Proposal for inclusion submitted by:

Bundesministerium für Ernährung und Landwirtschaft (BMEL)
Federal Ministry of Food and Agriculture
Referat 311
(German Codex Contact Point)
Wilhelmstr. 54
10117 Berlin
Germany
Phone: +49-(0)30-18529-3515
E-Mail: codex.germany@bmel.bund.de

2. Name of substance; trade name(s); chemical name(s):

Name of substance : Basic Methacrylate Copolymer, INS 1205

Trade names : Eudraguard® protect

Chemical names : Poly(butyl methacrylate-co-(2-dimethylaminoethyl)methacrylate-comethyl methacrylate) 1:2:1, CAS number 24938-16-7

3. Names and addresses of basic producers:

Manufacturer:

Evonik Röhm GmbH
Kirschenallee
64293 Darmstadt
Germany

Marketer:

Evonik Nutrition & Care GmbH
Kirschenallee
64293 Darmstadt
Germany

4. Has the manufacturer made a commitment to provide data?

Evonik Nutrition & Care GmbH commits to provide data to support the proposal for inclusion of Basic Methacrylate Copolymer in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Evonik Nutrition & Care GmbH
Kirschenallee
64293 Darmstadt
Germany

6. Justification for use:

Glazing agent / coating agent. „The technological function of the substance is to provide moisture protection and to mask the taste of various nutrients present in the treated products.“ (EFSA opinion, p. 7, „*Summary*“)

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

Food category: 13.6, food supplements
Max. use level: 100,000 mg/kg (10%)

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (Please identify the country(ies))

EU: EU food additive list, (Reg. (EC) No. 1333/2008), Annex II: E 1205 (amendment for E 1205 by Reg. (EC) No 1129/2011). EFSA opinion attached.

US: GRAS status (according to Section 201(s) of the FDC Act): Self affirmed (June 2012), at a level of up to 10% by weight of the supplement. GRAS notice attached.

Other countries: product registration in progress / in preparation

9. List of data available (please check, if available)

Toxicological data

„Basic methacrylate copolymer is virtually not absorbed from the gastrointestinal tract after oral administration. This is in line with it being a stable high-molecular compound.“ (EFSA opinion, p. 7, „*Summary*“)
The EFSA opinion on Basic Methacrylate Copolymer and the publication *Characterisation and toxicological behaviour of Basic Methacrylate Copolymer for GRAS evaluation* in the journal **Regulatory Toxicology and Pharmacology** ("RTP article"; both attached) provide details on the toxicological assessment.

(i) Metabolic and pharmacokinetic studies

See EFSA opinion, chapter 3.1, and RTP article, chapter 3.1. Quotation from EFSA opinion:

„An absorption, distribution, metabolism and excretion (ADME) study was performed with adult male rats (Charles River CD) in two phases. (...)

It was found that a mean total of 93.3% of the dose was eliminated via the faeces, mostly occurring within 48 hours after dosing. Similar values for recovery were obtained when faeces from untreated animals were spiked with the radiolabelled substance.

Excretion in urine was low, a mean total of 0.013% of the dose being excreted over the 5-day period following dosing. Although levels of radioactivity in urine were close to background levels, they were increased relative to controls 24 hours post-dose. This results in the conclusion that minor absorption from the gastro-intestinal tract may occur at less than 0.02% of the administered dose. Analysis of blood and tissues indicate that no significant amount of any absorbed material was retained.“

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

See EFSA opinion, chapter 3.2.2 – 3.2.5, and RTP article, chapter 3.2 – 3.4.

Selected quotations from the EFSA opinion:

- Short term toxicity:

A study was conducted with Beagle dogs for 28 days. "The Panel notes that the study was conducted in compliance with GLP. The Panel noted that there is no OECD guideline for a 28-day oral toxicity study in dogs available, and that, according to the applicant, the OECD guidelines no.407 (Repeated Dose 28-Day Oral Toxicity Study in Rodents) and no. 409 (Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents) have been considered. (...)"

"The Panel considered 750 mg/kg bw/day, the highest dose tested, as the No-Observed-Adverse-Effect Level (NOAEL) as the few changes that were observed including the changes in body weight and food consumption following oral administration for a period of 28 days were not toxicologically relevant."

- Sub-chronic toxicity:

A study was conducted with Sprague-Dawley rats for 26 weeks. "The petitioner points out that the study was carried out in 1973 when OECD and GLP guidelines were not yet implemented. However, the petitioner indicates that the study was undertaken by a recognised research organisation and the information available in the report indicates that the study was undertaken to standards generally in accordance with the requirements of OECD Test Guideline No.408. (...) The Panel considered that the NOAEL was 2000 mg/kg bw/day, the highest dose tested."

- Genotoxicity:

„Based on negative results derived from a gene mutation assay in *Salmonella typhimurium*, an *in vitro* mammalian cell gene mutation assay in L5178Y mouse lymphoma cells and an *in vivo* micronucleus assay, each performed according to current OECD guidelines and in compliance with GLP, the Panel concludes that basic methacrylate copolymer does not raise concern with respect to genotoxicity.“ (Source: chapter 4., Discussion)

- Chronic toxicity and carcinogenicity:

„No data were provided on chronic toxicity, however, given the high-molecular-weight of the substance and its lack of absorption, the EFSA panel considered that such data were not required.“ (Source: chapter 4., Discussion)

- Reproduction and developmental toxicity:

"There was no evidence of an effect of treatment on maternal animals."

"There were no effects on fetal survival as indicated by the extent of pre- and post-implantation loss (...) and the mean numbers of live fetuses (...). Fetal and placental weights were unaffected by treatment and so were the incidences and types of major fetal abnormalities. No treatment related effects were detected on the numbers of skeletal and visceral minor abnormalities and variants. The authors concluded the NOAEL for both dams and fetuses to be 1000 mg/kg bw/day."

"The petitioner did not provide data from studies on reproductive toxicity."

(iii) Epidemiological and/or clinical studies and special considerations

See EFSA opinion, chapter 3.2.6, and RTP article, chapter 3.6. Quotation from EFSA opinion:

„No studies in humans have been provided. However, the petitioner indicates that the basic methacrylate copolymer is currently used as a pharmaceutical excipient and that, although it is widely used, no clinical trials have been specifically performed using the substance alone. The petitioner points out that basic methacrylate copolymer are a construct from methacrylate monomers. It is not a protein and has not been shown to form conjugates with endogenous proteins. The petitioner argues that the many years of use of the substance as an excipient in pharmaceutical preparations has not revealed immunotoxic effects in the human population. The petitioner therefore, considers that there is no concern regarding allergenicity.“

The same is discussed a little bit more detailed in the RTP article.

(iv) Other data

None.

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

See EFSA opinion, chapters 2.1, Identity of substance, and 2.2., Specification, and commercial specification.

The product conforms to the specification as listed in Reg. (EU) No. 231/2012, with the exception of the particle size. The data named in the regulation were included there due to a misunderstanding. The correction of the particle size data is initiated at EFSA, see attached correspondence. The correct data are:

Particle size of powder: < 50 µm at least 95 %
 < 20 µm at least 50 %
 < 3 µm not more than 10 %

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

See below, intake assessment data.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

See EFSA opinion, chapter 2.6., Case of need and proposed uses. Quotation:

„Basic methacrylate copolymer is intended to be used as a glazing agent/coating agent in solid food supplements as defined in European Parliament and Council Directive 2002/46/EC and in solid foods for special medical purposes as defined in Commission Directive 1999/21/EC. The use is therefore restricted to products in dosage form, namely forms such as capsules, pastilles, tablets, pills and other similar forms like pellets, and powders. (...)“

„The petitioner indicates that only low use levels for coating are needed and that taste masking and moisture protection can be achieved with coating levels of 1-5 mg basic methacrylate copolymer /cm², equivalent to approximately 6 - 30 mg/tablet (for a tablet weight of 1000 mg). According to the petitioner the highest coating level could be up to 100 mg/ tablet (1000 mg).“

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

See EFSA opinion, chapter 2.8. (quoted below), and RTP article, chapter 4.1., Exposure.

In the EFSA opinion, the exposure to basic methacrylate copolymer is extensively discussed. As a conclusion for use in food supplements, „the anticipated exposure to basic methacrylate copolymer would be 2 mg/kg bw/day and 3 mg/kg bw/day respectively for adults and approximately 2.4 mg/kg bw/day for children", based on a normal coating level of 30 mg/tablet. „Taking into account a tablet weight of 1000 mg and a highest coating amount up to 10% weight per unit, for a 60 kg adult this consumption would lead to an anticipated exposure to basic methacrylate copolymer of 6.7 mg/kg bw/day and 10.0 mg/kg bw/day, respectively for average and heavy users. For children, assuming a body weight of 25 kg, the potential exposure would be approximately 8 mg/kg bw/day.“

„Furthermore, the petitioner also provided exposure estimates to basic methacrylate copolymer from use in pharmaceuticals. (...)The Panel assumed similar levels of use and intake of pharmaceutical products and supplements per day (EFSA, 2005). Given this assumption, the Panel estimated that the combined intake from food supplements and pharmaceutical products would be twice as high as the estimated intake for supplements only and would amount respectively to 16 mg/kg bw/day for children and to 23.3 mg/kg bw/day for adults (for a coating level of 100 mg methacrylic copolymer/tablet) and to 4.8 and 7.0 mg/kg bw/day, respectively (for a coating level of 30 mg methacrylic copolymer/tablet).“

Other information (as necessary/identified)

None

10. Date on which data could be submitted to JECFA

As soon as necessary.

Attachments:

1. BMC_Commercial specification_Eudraguard protect.pdf
2. BMC_EFSA opinion.pdf
3. BMC_EFSA request on particle size.pdf
4. BMC_Evonik reply on particle size.pdf
5. BMC_RTP article.pdf
6. BMC_GRAS notice.pdf

