

**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.*

<b>Name of Substance(s):</b>	<b>Neutral Methacrylate Copolymer</b>
<b>Question(s) to be answered by JECFA</b> <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](mailto:codex.germany@bmel.bund.de)

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

*Name of substance:* Neutral Methacrylate Copolymer, INS 1206

*Trade names:* Eudraguard® control

*Chemical names:* Poly(ethylacrylate-co-methyl methacrylate) 2:1, CAS number 9010-88-2

**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 Neutral 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 for sustained release formulations of nutrients in solid food supplements. Sustained-release formulations allow the continuous dissolution of a nutrient over a defined time.

**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: 200,000 mg/kg (20%)

**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 1206 (amendment for E 1206 by Reg. (EC) No 816/2013). EFSA opinion attached.

US: GRAS status (according to Section 201(s) of the FDC Act): Self affirmed (January 2014), at a level of max. 20 wt % in unit dosage. GRAS notice attached.

Other countries: product registration in progress / in preparation

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

***Toxicological data***

Neutral methacrylate copolymer is essentially not absorbed, and any absorbed material is not retained in the tissues. - The EFSA opinion on Neutral Methacrylate Copolymer and the publication *Characterisation and toxicological assessment of Neutral 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 ADME study was performed with adult male rats (Charles River CD) in two phases. (...)

The major route of excretion was via the faeces. A mean total of 97.2% (range: 93.6-101.7%) of the dose was eliminated via this route, mostly occurring within the 48 hours following dosing. Urine showed very low levels of elimination (0.009% of the administered dose). Extremely low levels of radioactivity were recovered from the blood and a number of tissues, resulting in the conclusion that absorption from the gastro-intestinal tract was less than 0.02% of the administered dose. Analysis of blood and tissues did not indicate that significant amounts of any absorbed material were retained. From the data it can be concluded that the polymer is essentially not absorbed and that any absorbed material is not retained in the tissues.“

(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 (chapters named above or chapter 4., Discussion):

- Short term toxicity:

„No specific changes occurred during the study that were attributed to treatment and (...) the No-Observed-Adverse-Effect Level (NOAEL) identified in this study may be regarded as 2000 mg/kg bw/day, the highest dose tested (...). The Panel agrees with this NOAEL.“

„A study with minipigs was conducted in accordance with to EEC Council Directives 65/65 and 75/318 and subsequent amendments. "Following the 4 weeks of treatment, no toxicologically relevant changes were observed in body weight, food consumption, clinical observations, and clinical pathology investigations and in the organ weights. Histopathological examination revealed sporadic instances of mucosal / submucosal oedema in the caecum and colon of one male receiving 454 mg/kg bw/day and in the caecum of one male dosed at 227 mg/kg bw/day. According to the authors of the study, the effect of the high doses is unclear and the finding may be a physiological reaction of the intestine to the high amounts of non-soluble or non-degradable particles resulting in osmotic imbalance in this part of the intestine. According to the authors, no toxicological relevance could be attributed to this observation (Rossiello, 2006). The Panel agrees with this conclusion and identified a NOAEL of 454 mg/kg bw/day."

- Sub-chronic toxicity:

„The results of the study show that the test substance, administered in the diet at dose levels up to 2000 mg/kg bw/day for 26 weeks was generally well tolerated. No treatment-related effects were noted on body weight, body weight gain, and food or water consumption. No clinical signs were apparent to indicate a treatment-related effect. Haematology and clinical chemistry parameters were not affected. No macroscopic or microscopic abnormalities were noted that were deemed to be a result of treatment. From the study the authors derived a NOAEL of 2000 mg/kg bw/day, the highest dose tested (...). The Panel agrees with this NOAEL.“

"The petitioner provided also data of another 26 weeks study with Beagle dogs. (...) According to the authors, the lower body weights and the reduced food consumption observed at the highest dose tested, could be explained by the characteristics of the test substance and were not accompanied by any signs of toxicity to organs or tissues, a NOAEL of 250 mg neutral methacrylate copolymer/kg bw/day, the highest dose tested (...). The Panel agrees with this NOAEL."

- Genotoxicity:

„From the *in vitro* Ames and mammalian cell mutation assays and the micronucleus assay *in vivo*, the Panel considers that neutral methacrylate copolymer does not raise concern with respect to genotoxicity.“

- Chronic toxicity and carcinogenicity:

„The Panel noted that the petitioner did not provide data on reproductive toxicity, chronic toxicity and carcinogenicity. In the absence of these data, chronic effects in the gastrointestinal tract following oral administration cannot be excluded. Therefore, the Panel considers that an ADI should not be established and that a margin of safety (MOS) approach is appropriate.“

- Reproduction and developmental toxicity:

„The petitioner did not provide data from one or two generation reproductive toxicity studies. The petitioner provided data of two studies focussing on prenatal developmental toxicity. The Panel noted that the

studies were carried out in 1974. The methods used were those described by the guidelines for reproductive studies for safety evaluation of drugs for human use of the FDA (1966) and the principles for the testing of drugs for teratogenicity, WHO, 1967. There were no indications that the studies were conducted in compliance with GLP. (...) The authors concluded the NOAEL for both dams and fetuses to be 2000 mg/kg bw/day. The Panel agrees with this NOAEL.“

(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 neutral 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.“

Quotation from RTP article:

„Although it is widely used, no human volunteer studies or clinical trials have been specifically performed investigating the substance itself. The substance does, however, have a history of use as a pharmaceutical excipient in Europe, the USA and Japan. All these pharmaceutical preparations are subject to national and/or European pharmacovigilance systems. No adverse effects have ever been reported to the manufacturer from these systems with regard to the consumption of drugs formulated with NMC.“

(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.

(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:

"Neutral methacrylate copolymer is intended to be used as a sustained-release glazing agent/coating agent in solid food supplements. Sustained-release formulations allows the continuous dissolution of a nutrient over a defined time. Neutral methacrylate copolymer is insoluble in aqueous media over the complete pH range. The sustained-release functionality is obtained via the permeability of the coating for the

nutrients in aqueous media. The addition of organic solvents is not necessary. The petitioner indicates that coating is done at temperatures in the range of 25 °C - 35 °C."

„The petitioner indicates that the amount of neutral methacrylate copolymer as glazing agent can be adjusted to the formulation to achieve sustained-release functionality. The sustained-release functionality can be achieved with a polymer amount of 10%. By increasing the polymer amount of the coating, the release profile can be modified to provide lower or higher release rates. It is indicated that the conventional polymer amount for a sustained-release profile is in the range of 10% to 20% (16.7 – 33.4 mg/cm<sup>2</sup>), equivalent to approximately 100-200 mg/tablet (for a tablet weight of 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., and RTP article, chapter 4.1., Exposure. Quotation from EFSA opinion:

„The petitioner provided an exposure assessment for (200 mg/tablet) using 2 supplements and 3 pharmaceutical pills per day for average user adults (3 supplements/day for heavy users) and 1 supplement and 1 pharmaceutical pill per day for children above 6 years. The total anticipated exposure from its combined use in solid food supplements and pharmaceutical pills of 200 mg/tablet would amount to either 16.7 mg/kg bw/day of neutral methacrylate copolymer for average adult users (i.e. 200 mg x 5 tablets), to 20 mg/kg bw/day for heavy adult users (i.e. 200 mg x 6 tablets), and to 16 mg/kg bw/day for children (i.e. 200 mg x 2 tablets), respectively. The Panel noted that the estimates provided by the petitioner are (slightly) lower than the estimates made on assumptions used by the Panel in previous evaluations (EFSA, 2004; EFSA, 2005). Data from the UK Food Standard Agency on the consumption of food supplements indicate that the use among high consumers (97.5th percentile) ranged from 2 tablets/capsules per day in young people (4-18 years) (Gregory, 2000) to 7 tablets/capsules per day in adults (Henderson et al., 2002). Therefore, the Panel calculated an anticipated exposure to neutral methacrylate copolymer (see Table 2) from its combined use in solid food supplements and pharmaceutical pills of 46.7 mg/kg bw/day of neutral methacrylate copolymer for high adult consumers (based on a coating of 200 mg/tablet) and of 32 mg/kg bw/day for children, respectively. Assuming a coating level of 200 mg methacrylate copolymer per tablet, the anticipated total exposure for high consumers resulted in 2800 mg/day (200 mg x 14 tablets) and 800 mg/day (200 mg x 4 tablets) of neutral methacrylate copolymer for adults and children, respectively.“

***Other information (as necessary/identified)***

None

**10. Date on which data could be submitted to JECFA**

As soon as necessary.

**Attachments:**

1. NMC\_Commercial specification\_Eudraguard control.pdf
2. NMC\_EFSA opinion.pdf
3. NMC\_RTP article.pdf

