Biocidal Products Committee (BPC)

Opinion on a request according to Article 75(1)(g)

Eligibility of peanut butter as active substance for inclusion into Annex I to the BPR

ECHA/BPC/307/2021

Adopted

1 December 2021

Opinion of the Biocidal Products Committee

on the eligibility of peanut butter as active substance for inclusion into Annex I to the BPR

In accordance with Article 75(1)(g) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products, the Biocidal Products Committee (BPC) has adopted this opinion on the eligibility of peanut butter as active substances for inclusion into Annex I to the BPR.

This document presents the opinion adopted by the BPC, having regard to the conclusions of the rapporteur.

Process for the adoption of opinion

A request of the Commission was received by ECHA on 22 June 2021. ECHA was appointed as the rapporteur at BPC-40. The rapporteur presented the draft opinion to the BPC at its meeting of 29 November – 3 December 2021. Following the adoption of the opinion at the BPC meeting of 1 December 2022 the opinion was amended according to the discussions at the meeting.

Adoption of the opinion

Rapporteur: European Chemicals Agency (ECHA)

The BPC opinion was adopted on 1 December 2022.

The BPC opinion was adopted by consensus.

The opinion is published on the ECHA web-site at: https://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/opinions-on-article-75-1-g.

Further details of the opinion and background

1. Request for the opinion and background

Article 28(1) of Regulation (EU) No 528/2012 (the BPR) empowers the Commission to adopt delegated acts in order to include active substances into Annex I to the BPR after receiving the opinion of ECHA, provided that there is evidence that they do not give rise to concern according to the conditions set out in Article 28(2).

Under Article 15(b), Regulation (EU) No 1062/2014 (the Review Programme Regulation) provided companies with an opportunity to support those active substances that benefitted from the food and feed derogation provided for by Article 6 of Regulation (EC) No 1451/2007. A declaration of interest (DoI) to notify had to be submitted to ECHA by 30 October 2015. ECHA finalised the review of these declarations in 2016 and concluded on their acceptability or refusal, which has been communicated to the related submitters.

ECHA published a list of declarations of interest to notify a substance which is eligible for inclusion in the review programme was published on the ECHA website and notifications according to Article 17 of the Regulation (EU) No 1062/2014 were submitted within 6 months from the date of its publication.

During the processing of the DoI and the notifications, ECHA was able to identify food and feed that are active substances and eligible for inclusion in the review programme as existing active substances. One of these substances could be peanut butter.

It was also considered that peanut butter might be a suitable candidate for inclusion into Annex I to the BPR, as it might not give rise to concern in accordance with Article 28(2) of the BPR. Peanut butter is applied as an attractant.

At the 91st meeting of representatives of Member States Competent Authorities for the implementation of Regulation (EU) No 528/2012 of 10-11 March 2021, it was agreed that the Commission will request a formal opinion of ECHA in order to check whether peanut butter is eligible for inclusion into Annex I to the BPR.

Pursuant to Article 75(1)(g) of Regulation (EU) No 528/2012, ECHA is therefore requested to formulate an opinion addressing the following questions:

1) Does the active substance not give rise to concern in accordance with Article 28(2) of the BPR, and is it therefore eligible for inclusion into Annex I?

2) If the active substance is eligible for inclusion into Annex I, is the active substance a traditionally used substance of natural origin?

Elements that will be provided by ECHA to answer question 2) will be useful to decide in which category the active substance may be included in Annex I.

2. Procedure

Article 16(1)(b) required companies to submit a declaration of interest to notify a substance which was eligible for inclusion in the Review Programme for a substance which benefitted from the derogation for food and feed provided for by Article 6 of Regulation (EC) No 1451/2007. Declarations of interest according to Article 16(1)(b) could be submitted to ECHA until 30 October 2015.

In that context, a notifier submitted a declaration of interest to notify peanut butter. The notifier then submitted a notification for peanut butter. The Agency verified the notification according to Article 17(5) of Regulation (EU) No 1062/2014 and rejected it because the Agency found that the notification did not comply with the data requirements laid down in Annex I to the Review Programme Regulation.

In 2017, the notifier brought the case to the ECHA Board of Appeal (case number A-13-2017) that annulled the decision of the Agency and instructed it to examine the eligibility of peanut butter for inclusion in the review programme as per its interpretation of Article 15 of the Review Regulation. According to the Board of Appeal, the Agency should have assessed whether the following conditions stemming from Article 15 of the new RPR were met:

a) the substance for which the Declaration of Interest was submitted is an existing active substance that was neither approved, nor included, in the Review Programme or Annex I to the BPR,

b) the existing active substance benefited from the derogation for food and feed under the previous RPR,

c) the product which consists of, contains or generates the existing active substance is a biocidal product falling within the scope of the BPR, and

d) the biocidal product is placed on the market.

In December 2020, the Agency informed the notifier that peanut butter fulfils the requirements of Article 15 of the Review Regulation and requested the notifier to submit a new notification. ECHA verified the received notification and found it compliant. The Commission was informed thereof. The Agency updated its list of compliant notifications accordingly. The final decision to include an active substance in the Review Programme will be adopted by the European Commission in accordance with Article 18 of Regulation (EU) No 1062/2014.

At the 91st meeting of representatives of Member States Competent Authorities for the implementation of Regulation (EU) No 528/2012 of 10-11 March 2021, it was agreed that the Commission will request a formal opinion of ECHA in order to check whether peanut butter is eligible for inclusion into Annex I to the BPR.

On 22 June 2021, the Commission requested ECHA to provide its opinion on the eligibility of peanut butter (no CAS and no EC number) as active substances for its inclusion into Annex I to the BPR.

3. Approach followed

3.1 Identification of the active substance ‘peanut butter’

Peanut butter is defined as an UVCB substance, hence an active substance of unknown or variable composition, complex reaction products or biological material. According to the information provided for the notification the chemical composition of peanut butter comprises:

- fats (~60%);
- proteins (~28%);
- sugars (~8.4%);

- minerals (~2.1|%);
- water (~1%).

These chemical groups were further analysed for individual compounds. Thus, the analyses provide a reasonable overview of the chemical composition of peanut butter.

3.2 Data sources and consultations used

Annex A, Section A, to the Regulation (EU) No 88/2014 lists the data requirements for the inclusion of active substances in Annex I to the BPR. Paragraph 1(b) states that the applications shall contain conclusive evidence to demonstrate that there is a robust consensus of expert opinion that the active substance does not give rise to concern in accordance with Article 28(2) of the BPR.

In order to demonstrate this robust consensus of expert opinions, the Regulation (EU) No 88/2014 provides a list of data sources that shall be used. That includes, among others, all relevant published literature references regarding the active substance in question, all relevant information on the active substance generated by the notifier and conclusions from other regulatory authorities or frameworks.

For the purpose of this opinion, ECHA has followed the same approach to ensure robust consensus of expert judgment and to demonstrate methodological consistency. Accordingly, to assess if peanut butter would give rise to concern in accordance with Article 28(2), ECHA used all the information available in the declarations of interest to notify, information submitted in the notifications, the Classification and Labelling Inventory and other bibliographic information easily accessible to ECHA (please refer to the list of references). In addition, the conclusions from other regulatory authorities or frameworks, European and international, have been used.

Information concerning EU frameworks was extracted from:

- Regulation (EC) No 178/2002 - Food Law;
- Regulation (EU) No 1169/2011 [1] on the provision of food information to consumers.

The information regarding the non-EU frameworks was mainly taken from international databases and governmental web inventories.

Having compiled this information, ECHA identified possible concern raised by peanut butter properties for specific toxicological endpoints. ECHA launched in August 2021 an e-consultation with the Working Group – Human Health (WG – TOX) members and the notifier, requesting their views on whether peanut butter meets the Article 28(2) criteria for these endpoints in order to assist the SECR in delivering its opinion, NL and DE provided comments. The questions of the e-consultation were brought to the WGIII2021-TOX meeting in September 2021 for additional input by the members. The notifier provided comments after the WG discussion.

3.3 Elements considered by ECHA

3.3.1 With regard to the question, does the active substance not give rise to concern in accordance with Article 28(2) of the BPR, and is it eligible for inclusion into Annex I?

Article 28 of the BPR defines the specific criteria concerning the properties that active

substances shall not have to be listed in Annex I. According to Article 28(1) and (2), active substances can be included in Annex I if there is evidence that they do not give rise to concern.

According to Article 28(2) a substance is considered to give rise to concern where:

(a) it meets the criteria for classification according to Regulation (EC) No 1272/2008 as:

- Explosive/highly flammable
- Organic peroxide
- Acutely toxic of category 1, 2 or 3
- Corrosive of category 1A, 1B or C
- Respiratory sensitizer
- Skin sensitiser
- Germ cell mutagen of cat 1 or 2
- Carcinogen of cat 1 or 2
- Human reproductive toxicant of category 1 or 2 with effects on or via lactation
- Specific target organ toxicant by single or repeated exposure
- Toxic to aquatic life of acute category 1

(b) it fulfils any of the substitution criteria set out in Article 10(1); or

(c) it has neurotoxic or immunotoxic properties.

An active substance also gives rise to concern, even if none of the specific criteria in points (a) to (c) are met, where a level of concern equivalent to that arising from points (a) to (c) can be reasonably demonstrated based on reliable information.

The available data for peanut butter were evaluated using the criteria of the BPR. The summaries with the relevant information to assess if peanut butter would give rise to concern in accordance with Article 28(2) are included in Annex I to this opinion. In summary, information was found about 4 endpoints of concern according to the Art. 28(2): skin and respiratory sensitisation, immunotoxicity and carcinogenicity.

The assessment performed in accordance with the Art. 28(2) criteria is in line with the outcome of discussion of WG III 2021-TOX and concluded that peanut putter raises concern for immunotoxicity as food causing allergies. The allergies can be induced not only by the oral route of exposure but also by the dermal route, whereas cross reactivity of peanut butter with other substances or food causing allergies can increase the incidence of allergies.

For the endpoints of skin and respiratory sensitisation and carcinogenicity, it was concluded that peanut butter does not meet the criteria for classification according to CLP Regulation and consequently, does not give rise to concern for these properties in accordance with Art. 28(2) of the BPR.

The evaluation of all Art. 28(2) criteria regarding the physicochemical, toxicological and environmental properties of peanut butter is included in the Factsheet.

Overall, it is concluded that the active substance 'peanut butter' causes allergies and gives rise to concern for immunotoxicity according to Article 28(2) of the BPR, and that the dermal route of exposure can also elicit skin reactions and may contribute to sensitisation to peanut allergens. Subsequently, it is concluded that peanut butter cannot be included to Annex I of the BPR.

3.3.2 Consideration of possible risk management measures or restrictions for peanut butter

During the discussions in the Human Health Working Group (WG TOX) and the BPC, several possible risk management measures (RMMs) and restrictions were discussed in the context of assessing whether peanut butter was eligible for inclusion in Annex I, since this would have resulted in peanut butter be allowed for use in biocidal products without a detailed assessment according to the simplified authorisation procedure.

As it was concluded that peanut butter is not eligible for inclusion in Annex I of BPR, the discussed RMMs and restrictions are listed below for consideration in the evaluation of a subsequent application for peanut butter as an active substance under the BPR:

- harmonisation with Regulation (EU) No 1169/2011 on the provision of food information to consumers as condition for the approval of peanut butter, i.e. including on the label of the biocidal product and/or the packaging (including refill packages) that it contains peanut butter (condition widely supported by HH WG and BPC members);
- the addition of a dye and bittering agent to peanut butter;
- restriction of use in RTU (ready to use) products, such as child resistant traps for rodents and insects to mitigate the exposure.

3.3.3 If the active substance is eligible for inclusion into Annex I, is the active substance a traditionally used substance of natural origin?

Annex I to the BPR includes as category 4 traditionally used substances of natural origin. As these terms do not refer to a legally binding definition of the BPR, the following considerations were applied for deciding whether peanut butter can be allocated to this category:

Substance of natural origin

The REACH Regulation (EC) No 1907/2006 provides the definition for 'substance that occur in nature' as substances which occur in nature' means 'a naturally occurring substance as such, unprocessed or processed only by manual, mechanical or gravitational means, by dissolution in water, by flotation, by extraction with water, by steam distillation or by heating solely to remove water, or which is extracted from air by any means'.

In addition, the European inventory of existing commercial chemical substances (EINECS) includes the entry with the EC number 310-127-6 and CAS number 12001-26-2 for 'Naturally occurring substances' that are defined as "Living or dead material occurring in nature as such which is chemically unprocessed, or which is extracted from air by any means or physically processed only by manual, mechanical or gravitational means, by dissolution in water, by flotation or by heating solely to remove water."

The manufacturing process of peanut butter must be considered for deciding whether these definitions apply to it and peanut butter can be regarded as a substance of natural origin.

The notifier of peanut butter provided the following information about the manufacturing process:

“Peanut butter is defined as an active UVCB substance retrieved by the roasting process of peanuts, which are then subsequently mechanically crushed in to a “butter”. The manufacturing process of peanut butter consists of several key steps under which the processes of roasting, skin peeling and crushing into a butter define this UVCB substance’s chemical identity. During the roasting process several different types of chemical reactions takes place, which all define the composition of “peanut butter” as an UVCB substance, whilst the processes of peeling and crushing mainly define the physical and chemical properties of the “peanut butter” (e.g. viscosity and density). Peanut butter as a “UVCB-substance” is defined by the following identification parameters and criteria: (i) the specific origin of the raw material – peanuts, seeds of the groundnut (Arachis hypogaea L.); and (ii) the processes in which the chemical reactions or synthesis of new molecules are involved, under which the UVCB substance “peanut butter” is obtained (i.e. the roasting process, normally taking place at 145 – 175 °C depending on the moisture content, including the post processes of skin peeling and crushing into a butter which changes the physical and chemical properties of the roasted peanuts).”

The peanut as such is dead a material occurring in nature as such which is chemically unprocessed, and processed only by manual, mechanical or gravitational means. However, the roasting can be regarded as heating which does not serve solely to remove water. In fact, the notifier describes roasting as thermal composition reactions, non-enzymatic carbonyl-amine browning reactions and caramelization reactions. Consequently, peanut butter is not a substance which occur in nature or a naturally occurring substance and also not a substance of natural origin. The steps following the roasting procedure, crunching or grinding to release the peanut oil from plant fat cells are mechanical processing steps that would be again covered by the definitions a substance which occur in nature or a naturally occurring substance.

Traditionally used substance

The Cambridge Dictionary defines ‘tradition’ as “a belief, principle, or way of acting that people in a particular society or group have continued to follow for a long time, or all of these beliefs, etc. in a particular society or group”; the American dictionary defines ‘tradition’ as “a way of behaving or a belief that has been established for a long time, or the practice of following behaviour and beliefs that have been so established”.

In the context of this document the term ‘traditionally used’ it should be decided and interpreted whether peanut butter is traditionally used for biocidal purposes. The traditional use of peanut butter would mean that there is an established practice for a long time for the use of peanut butter as attractant in biocidal products used in mechanical rodent traps.

Although an internet search engine with key search terms:

- “peanut butter attractant for rodents”;
- “peanut butter attractant for insects”;
- “peanut butter homemade bait ant cockroach”;

confirms that peanut butter is widely used as an attractant for rodents and insects it remains unclear whether the time since this use has been established, can be regarded sufficiently long to be regarded as ‘traditional’. In addition, it remains also unclear whether peanut butter as attractant is applied in all member states of the EU. Consequently, peanut

butter should not be included in the category of traditionally used substance of natural origin of Annex I to the BPR.

4. Overall conclusions

As peanut butter has immunotoxic properties, it should be regarded as a substance which gives rise to concern according to Article 28(2) of the BPR and therefore it cannot be included in Annex I.

Peanut butter is a substance of natural origin but not a traditionally used substance, noting there is no definition under the BPR nor other EU legislation of “traditionally used substances”.

Annexes

Information

To assess if peanut butter gives rise to concern in accordance with Art. 28(2), ECHA has used:

I. **Information available in the declarations of interest to notify**

II. **Information submitted in the notification**

III. **The statement submitted by the notifier for the notification of peanut butter as PT19 attractant**

IV. **The Classification and Labelling (C&L) Inventory of substances**

V. **Information from other regulatory authorities or frameworks, European and international.**

VI. **Bibliographic information (please refer to the list of references).**

VII. **The outcome of the TOX WG e-consultation in August 2021.**

VIII. **The outcome of the WG III 2021-TOX meeting discussion in September 2021.**

Assessment of Information

I. The notification includes the information that peanut butter is notified as PT19 Repellents-Attractants.

II. There is no information in the IUCLID dataset of the submission related to Art. 28(2) hazard assessment properties of peanut butter. There is only description of uses in treated articles: *Peanut butter is used as bait in special traps for rodents. The products are mechanical traps, but since the animals will be attracted by the prefilled bait, the products are biocidal products under PT 19.*

III. The notifier was requested by ECHA to provide its opinion on whether peanut butter gives concern in accordance with Art. 28(2) and is eligible for inclusion in Annex I of BPR.

The notifier's reply is found in Annex II of the current opinion. It includes 5 arguments regarding the eligibility of peanut butter for inclusion in Annex I. Each of the arguments are addressed below.

IV. Neither a harmonised nor self-classified classification is established for peanut butter in the ECHA C&L Inventory.

V. Information concerning EU and international frameworks and assessments was extracted from:

- Regulation (EC) No 178/2002 [3] - Food Law: peanut butter is considered food in accordance with the definition of "food" in article 2: *'food' (or 'foodstuff') means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans*.

The notifier argued that according to Art. 2 (5)a of BPR “This regulation should not apply to food or feed used as repellents or attractants”. The notifier does not understand “*why the interpretation of this Article was changed later so that products with food and feed should fall under the BPR*”.

ECHA notes that this issue was addressed in the Appeal (case number A-13-2017), where the Board of Appeal accepted ECHA’s defence based on the relevant CA document “Interpretation of the provisions of Article 2(5)(a) of Regulation (EU) No 528/2012”[i] according to which the exemption only applies to food "as such" i.e. in a kitchen cupboard, not food that is intentionally placed on the market with a biocidal purpose which is the case with this company's products.

- Regulation (EU) No 1169/2011 on the provision of food information to consumers includes “Peanuts and products thereof” in the list of “Substances or products causing allergies or intolerances“. Manufacturers of packaged food products that contain peanuts (or products thereof) have the obligation to include this information with clear and emphasised typeset on the package to protect sensitised individuals.

  In the same list of 1169/2011, “eggs and products thereof” are included. Powdered egg was included in Annex I of BPR without restrictions based on BPC opinion ECHA/BPC/186/2017.

- EFSA Scientific Opinion on the evaluation of allergenic foods and food ingredients (2014) [4], under section 18 “Allergy to peanuts”, pages 105-117, provides extensive information which includes also specific reference to peanut butter:

  “The wide uses of peanuts and derived products in processed foods make inadvertent exposure frequent. For example, peanut butter is often used in restaurants to harden soft foods or to glue down and close egg rolls. (…)

  Peanut is a common cause of allergic reactions, which can be severe or even fatal. (…)

  Peanut is the most common cause of severe or fatal food-induced anaphylaxis. The most severe reactions have been observed in subjects with asthma. (…)

  Prevalence of well documented peanut allergy in Europe varies between 0.1 to 1.8 % depending on the age and country of origin, whereas the available data do not allow concluding on whether the prevalence of peanut allergy has changed in the last years in Europe. The major peanut allergens are well characterised. Roasting may increase the IgE-binding capacity of peanut allergens, whereas boiling may decrease it or leave it unchanged. The lowest reported MOED in peanut allergic patients undergoing DBPCFC was 100 g of peanut protein, with a NOAEL of 30 g. However, few data are available on the doses which may trigger allergic reactions in highly sensitive patients, who are often excluded from challenge tests but tend to react to lower doses than patients with mild symptoms”.

- Under the US Food Allergen Labelling and Consumer Protection Act of 2004 [5], peanut is one of eight allergens (along with milk, egg, tree nuts, fish, wheat, soybeans, shellfish) with specific labelling requirements. Manufacturers of packaged food products that contain peanut as an ingredient that are sold in the U.S. must include the word “peanuts” in clear language on the ingredient label.

[i] CA-Dec13-Doc.11.3 – Final.rev1 (updated as per CA-March16-Doc.4.5)

- The Food Standard Code in Australian and New Zealand [6] includes peanut (along with tree nuts, milk, eggs, sesame seeds, fish, shellfish, soy, lupin and wheat) in the foods that can cause allergic reactions and requires suppliers to declare it on labels whenever present.

Overall, peanut butter is worldwide regulated as food causing allergies.

VI. The literature review search was performed in Pub Med and Science Direct with the words “peanut butter” in Title, Abstract and Keywords. From results the subject areas of “Chemistry” and “Chemical engineering” were excluded as relevant to quality characteristics, analysis of components, products development and removal of allergens which is not of interest for the assessment of potential concern raised by peanut butter in accordance with Art. 28(2). Therefore, the search was general to cover all criteria of Art. 28(2). The results of the literature search are included in the Literature Search file. The literature search results deserving further investigation for the assessment of the criteria of Art.28 (2) concern the following endpoints and are presented below in more detail:

- Skin sensitisation
- Respiratory sensitisation
- Carcinogenicity
- Allergy as part of part of immunotoxicity.

The information derived from the literature review is included in the assessment of each toxicological endpoint below.

Assessment of explosive / highly flammable – criterion (a) of Art. 28(2)

Flammability: There is not measurement of the flash point available for peanut butter. However, considering the analysed composition of peanut butter it can be concluded that the flash point of peanut butter is >60°C. Hence no classification as flammable liquids is required. The constituents of peanut butter are either solids or liquids with a measured or calculated flash point of >>150°C and with measured or calculated boiling points >100°C. Consequently, the flash point of peanut butter will not be in the relevant temperature range of <60°C and its boiling point will be >35°C.

Explosives: The constituents of peanut butter do not contain any functional group that are associated with explosive properties. Therefore, it can be concluded that peanut butter is not explosive.

Assessment of organic peroxide – criterion (a) of Art. 28(2)

None of the constituents of peanut butter contains a peroxy-group (-O-O-). Thus, it can be excluded that peanut butter belongs to the group of organic peroxides.

Assessment of skin sensitisation – criterion (a) of Art. 28(2)

Data from literature search

Skin sensitisation gives rise to a type IV hypersensitivity which is T cell-mediated and triggered by low molecular weight chemicals that have to be covalently bound to endogenic (skin) proteins to become immunogenic.

Recognised peanut allergens are proteins of the prolamin, profilin, cupin, and oleosin families, Bet v-1 related proteins, and defensin peptides [7] giving rise to food allergies which are Type I reactions that are antibody (i.e. IgE) mediated. Thus, it is considered unlikely that peanut butter could elicit skin sensitisation in a way that would lead to a delayed type (type IV) allergic contact dermatitis as is common for substances that are classified as skin sensitisers according to the GHS.

This is supported also by open literature where no reports of skin sensitisation reactions following epicutaneous exposure to peanut allergens are found.

In a study conducted to determine the frequency with which peanut-sensitive children exhibited contact sensitivity to peanut butter (Wainstein, 2007 [8]), the authors reported:

A minority of children sensitized to peanut (positive SPT) develop localized urticaria from prolonged skin contact with peanut butter. No tested subjects, including ones with systemic reactions upon oral challenge, developed a systemic reaction to prolonged skin exposure to peanut. Therefore, systemic reactions resulting from this mode of contact with peanut butter appear highly unlikely.

Outcome of WG TOX e-consultation and WGIII2021-TOX discussion

The members of WG TOX agreed that peanut butter does not give rise to concern for skin sensitisation in accordance with Art. 28(2) of the BPR.

Overall, it is concluded that peanut butter does not meet the criteria for classification for skin sensitisation according to CLP Regulation and consequently does not give rise to concern for this endpoint in accordance with Art. 28(2) of the BPR.

Assessment of respiratory sensitisation – criterion (a) of Art. 28(2)

Data from literature search

Respiratory sensitisation leads to type I reactions that are antibody (i.e. IgE) mediated and that also include food allergies. Peanut butter may therefore, theoretically, also trigger respiratory sensitisation if its allergens become airborne. In fact, peanut allergens can be detected in household dust [9, 10].

Yet, this is not supported by the available literature based on which it can be concluded that peanut antigens do not cause any respiratory reaction [11, 12]. In general, allergic reaction to airborne peanut proteins are considered to be extremely rare, since only very small amounts of active peanut proteins are detectable in the air [13].

Outcome of WG TOX e-consultation and WGIII2021-TOX discussion

At the time of the e-consultation and WGIII2021 discussion, ECHA conducted a preliminary literature review. The members of the WG TOX indicated that for respiratory sensitisation, which leads to antibody mediated type I reactions that also include food allergies, a complete literature search is needed to thoroughly assess this endpoint. The WG however agreed that based on the available data, peanut butter does not give rise to concern for respiratory sensitisation in accordance with Art. 28(2) of the BPR. ECHA conducted the complete literature review in October 2021.

Overall, and based on the results of the complete literature review, peanut butter does not meet the criteria for classification for respiratory sensitisation according to CLP Regulation

and consequently does not give rise to concern for this endpoint in accordance with Art. 28(2) of the BPR.

Assessment of carcinogenicity – criterion (a) of Art. 28(2)

Data from literature search

Open literature studies were found that investigated peanut butter intake and the risk of:

- colorectal cancer [14]. It was found that peanut butter intake is non-linearly inversely associated with rectal cancer risk in women. In men, peanut butter is associated with an increased risk of colorectal tumours that do not develop through the serrated neoplasia pathway in men;

- lung cancer [15]: No significant associations were found in men or women for lung cancer and peanut butter intake;

- oesophageal and gastric cancer [16]: It was found that among older American adults, peanut butter consumption was inversely associated with the risk of gastric noncardiac adenocarcinoma.

In addition, there are open literature studies investigating the exposure risk to carcinogenic aflatoxins [17], where the contamination levels of aflatoxins are reported to be much lower than the permitted. ECHA considered the studies on aflatoxins levels in peanut butter as not relevant for the assessment of criteria Art. 28(2), which focuses on the properties of the substance per se, and not on properties from food contaminants which depend on their growth and the post-harvest storage conditions of peanuts. Moreover, Regulation (EC) No 1881/2006[ii] sets the maximum limit of aflatoxins in foodstuffs in EU. Any food containing higher amounts should not be in the EU market. To ensure that food is safe for EU consumers, continuous monitoring including monitoring of aflatoxins levels, is in place along with other tools enabling swift reaction when risks to public health are detected in the food chain[iii].

Regarding the positive association of specific type of colorectal cancer (CRC) in men, ECHA notes that this result is based on the Netherlands Cohort Study (*n* = 120.852), where lifestyle habits were measured since 1986. After 20.3 years follow-up, 3567 CRC cases were included in case–cohort analyses. For the analyses of molecular CRC subtypes, 574 cases were included after 7.3 years follow-up. In the analysis, continuous consumption of 5g/day peanut butter was considered.

For the assessment of carcinogenicity – criterion (a) of Art. 28(2), it has to be assessed whether the above data warrant classification of peanut butter as human carcinogen in accordance with the CLP criteria based on which "*human studies should establish a causal relationship between human exposure to a substance and the development of cancer*". The positive association of peanut butter consumption with specific type CRC in men from one dietary survey in one country does not quality as such study.

Outcome of WG TOX e-consultation and WG III 2021-TOX discussion

Based on the outcome of the preliminary literature search, the TOX e-consultation and WG discussion in August and September 2021 did not include any question on the criterion of

[ii] COMMISSION REGULATION (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1881-20150731&from=EN

carcinogenicity, which was only identified as of potential concern in the complete literature search conducted by ECHA in October 2021. So there no input from WG TOX on this endpoint.

Overall, it is concluded that peanut butter does not meet the criteria for classification for carcinogenicity according to CLP Regulation and consequently does not give rise to concern for this endpoint in accordance with Art. 28(2) of the BPR.

Assessment of immunotoxic properties – criterion (c) of Art. 28(2)

Data from literature search

Peanut allergy is a frequent food allergy with point prevalences for a positive skin prick test ranging from 0.4 % to 5.1 % in Western Europe according to a comprehensive review of food allergy prevalences in the EU [18]. It is very common in atopic patients and patients suffering from more than one allergy [19]. Oral exposure to peanut allergens may pose a life-threatening risk to sensitised individuals by inducing severe systemic anaphylaxis following the ingestion of very small amounts of peanuts and peanut-containing products.

Regarding peanut allergy induced by other routes of exposure than oral, in almost all cases reported in open literature, skin reaction to peanut allergens is closely related to skin barrier dysfunction[20]. Children with atopic dermatitis will mostly develop a peanut allergy via their skin. The literature suggests that there is a strong corelation between patients suffering from eczema and the likelihood to develop a peanut allergy [9, 21-24].

Data provided by DE at the WG-TOX e-consultation

Some studies suggest that sensitisation to peanut allergens may take place through other than the oral route of exposure. These studies are confined to epicutaneous exposure eventually leading or contributing to peanut allergy as a food (i.e. type I) allergy [9, 20, 22, 23]. However, the underlying mechanism – epicutaneous exposure inducing a subsequent type I reaction – is not covered by the skin sensitisation endpoint and the respective AOP since the adverse outcome is not an allergic contact dermatitis but rather a food allergy.

This sensitisation path has also been experimentally confirmed in mouse models with disrupted and undamaged skin [22, 23]. In non-human primates, repeated epicutaneous exposure to peanut extract did not lead to sensitisation as evidenced by unchanged IgE levels but did induce an increase of peanut specific IgG, thus indicating an immunogenic response [24]. Thus, not only oral exposure has to be taken into account for risk assessment but also exposure via the skin.

Additionally, open literature studies indicate concern for cross-reactivity of peanut butter with other allergens. Cross-reactivity is a phenomenon well known for type I allergies where individuals sensitised to airborne antigens, e.g. tree pollen, also react to certain food allergens like apple proteins [25]. Mechanistically, cross-reactivity is elicited by structural or physico-chemical similarities (of the IgE binding site) between different food and/or airborne immunogenic proteins [7]. Peanut protein cross-reactivity has been shown for birch pollen [19], tree nuts and legumes (e.g. lupine) [7, 26]. Clinical data suggest that cross-reactivity between peanut and other allergens is bidirectional, so that sensitisation to peanut proteins may be cause and consequence of other allergic reactions [25, 26]. Such cross-reactions should therefore be regarded as immunotoxic responses that fall under the definition provided by BPR Guidance: “Immunotoxic responses may occur when the immune system is

[iii] RASFF - food and feed safety alerts: https://ec.europa.eu/food/safety/rasff-food-and-feed-safety-alerts_en

the target of the chemical insult; this in turn can result in […] immune dysregulation which exacerbates allergy" (Vol. III, parts B+C, section 1.7.3.3.1 Definition of immunotoxicity).

Data from notifier

Notifier submitted the following data regarding the allergic properties of peanut butter: "*The allergy to food is a very special form of allergy. Everybody allergic to peanuts knows it and is very careful to avoid oral intake or in a very severe form also dermal or inhalative exposure of anything where peanuts could be used. It is different from substances which potentially may cause allergic reactions. Tests revealed that 0.2 % of the Europeans express peanut allergy, in general a rate of 2 % is estimated. In consequence, 98 % of the Europeans are not allergic against peanuts. It is a very special genetic predisposition, not a general one. (…)*

Since food items were excluded from BPR it is obvious that food allergies are not covered. Data point 8.13.4 Immunotoxicity including developmental immunotoxicity belongs to the additional data set and has only to be addressed when there is any evidence from skin sensitisation, repeat dose or reproduction toxicity studies, that the active substance may have immunotoxic properties. Since in the case of peanut butter there is no such evidence, from a regulatory perspective this point is not relevant here".

Outcome of WG TOX e-consultation and WGIII2021-TOX discussion

The members of the WG TOX agreed that peanut butter has immunotoxic properties. There was no consensus between the members on whether the concerns included in Art. 28(2) can or cannot be mitigated with RMMs that restrict exposure.

ECHA assessment

The notifier did not provide references for the incidence of peanut allergy in Europeans stated above. As explained under point V on pages 9, 10, the food exemption from BPR does not apply for food placed on the market with a biocidal purpose. Therefore, peanut butter has to assessed in accordance with the criteria of Art. 28(2). Regarding the reference to point 8.13.4 of Annex II of BPR, ECHA notes that in the absence of animal studies for peanut butter, human data is used in accordance with 1.1.3 of Annex IV of BPR demonstrating the well know potential of peanut butter to cause food allergies.

According to the definition of immunotoxicity in the BPR Guidance Parts B+C:

"Immunotoxicity" is defined as any adverse effect on the immune system that can result from exposure to a range of environmental agents, including chemicals (WHO/IPCS, 2012). Immunotoxic responses may occur when the immune system is the target of the chemical insult; this in turn can result in either immunosuppression and a subsequent decreased resistance to infection and certain forms of neoplasia, or immune dysregulation which exacerbates allergy or autoimmunity. Alternatively, toxicity may arise when the immune system responds to an antigenic specificity of the chemical as part of a specific immune response (i.e. allergy or autoimmunity) (IPCS, 1996).

Based on the above definition, allergic reactions are considered as manifestation of immunotoxicity. As peanut butter causes allergies, it possesses immunotoxic properties.

The BPR guidance also indicates: The Guidance for Immunotoxicity risk assessment for chemicals by WHO/IPCS (WHO/IPCS, 2012) shall be consulted together with this Guidance when performing the assessment of this endpoint. In the WHO/IPCS, 2012 Guidance, sensitisation and allergic response are listed among the different types of immunotoxicity.

Due to its properties as a food allergen and noting the above definition and guidance, peanut butter is considered to have immunotoxic properties. Notably, the allergy and sensitisation can be induced not only by the oral route of exposure but also by the dermal route, whereas cross reactivity of peanut butter with other substances including airborne allergens (e.g. tree pollen) or food causing allergies can increase the incidence of allergic reactions.

Factsheet peanut butter

Property		**Conclusions**	
Physical hazards	Explosive	No classification required	Peanut butter does not fulfil criterion (a), of Article 28(2)
	Highly flammable	No classification required	
	Organic peroxide	No classification required	
Acutely toxic of category 1, 2 or 3	No classification required. Peanut butter does not fulfil criteria (a) of Article 28(2).		
Corrosive of category 1A, 1B or C	No classification required. Peanut butter does not fulfil criteria (a) of Article 28(2).		
Respiratory sensitisation properties	No classification required. Peanut butter does not fulfil criteria (b) of Article 10(1) and (a) of Article 28(2).		
Skin sensitiser	No classification required. Peanut butter does not fulfil criteria (a) of Article 28(2).		
CMR properties	Carcinogenicity (C)	No classification required	Peanut butter does not fulfil criterion (a), (b) and (c) of Article 5(1) and (a) of Article 28(2)
	Mutagenicity (M)	No classification required	
	Toxic for reproduction (R)	No classification required	
Specific target organ toxicant by single or repeated exposure	No classification required. Peanut butter does not fulfil criteria (a) of Article 28(2).		
Toxic to aquatic life of acute category 1	No classification required. Peanut butter does not fulfil criteria (a) of Article 28(2).		
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	Not P or vP	Peanut butter does not fulfil

	Bioaccumulative (B) or very Bioaccumulative (vB)	not B or vB	criterion (e) of Article 5(1) and does not fulfil criterion (d) of Article 10(1)
	Toxic (T)	not T	
Endocrine disrupting properties	Peanut butter is not considered to have endocrine disrupting properties		
Neurotoxic or immunotoxic properties	Peanut butter **is considered to have immunotoxic properties.** Peanut butter is not considered to have neurotoxic properties.		

Based on the available data, no classification is currently used or proposed for peanut butter concerning its physico-chemical, toxicological, environmental and ecotoxicological properties in accordance with the CLP Regulation 1272/2008 (criteria (a) Article 28(2)).

Peanut butter does not meet the exclusion criteria laid down in Article 5 of Regulation (EU) No 528/2012.

Peanut butter does not meet the conditions laid down in Article 10 of Regulation (EU) No 528/2012, and is therefore not considered as a candidate for substitution.

The exclusion and substitution criteria were assessed in line with the "Note on the principles for taking decisions on the approval of active substances under the BPR"[iv] and in line with "Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR"[v] agreed at the 54th and 58th meeting respectively, of the representatives of Member States Competent Authorities for the implementation of Regulation 528/2012 concerning the making available on the market and use of biocidal products. This implies that the assessment of the exclusion criteria is based on Article 5(1) and the assessment of substitution criteria is based on Article 10(1)(a, b, d, e and f).

It is concluded that peanut butter **gives rise to concern according to Article 28(2)(c) of the BPR due to its immunotoxicity.**

[iv] See document: Note on the principles for taking decisions on the approval of active substances under the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/c41b4ad4-356c-4852-9512-62e72cc919df/CA-March14-Doc.4.1%20-%20Final%20-%20Principles%20for%20substance%20approval.doc)

[v] See document: Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/dbac71e3-cd70-4ed7-bd40-fc1cb92cfe1c/CA-Nov14-Doc.4.4%20-%20Final%20-%20Further%20guidance%20on%20Art10(1).doc)

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Literature search

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Annex II – Statement of Notifier

applicant_statement.pdf

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