Biocidal Products Committee (BPC)

Opinion on a request according to Article 38 of Regulation (EU) No 528/2012 on

Question on an unresolved objection during a mutual recognition procedure in accordance with Article 36 (1) of Regulation (EU) No 528/2012 of a PT 18 biocidal product intended for the treatment of wasps and hornets nests

ECHA/BPC/367/2022

Adopted

23 November 2022

Opinion of the Biocidal Products Committee

on an unresolved objection during a mutual recognition of a PT18 permethrin containing biocidal product intended for the treatment of wasp/hornet nests

In accordance with Article 38 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 a question concerning an unresolved objection during a mutual recognition of a PT18 permethrin containing biocidal product intended for the treatment of wasp/hornet nests.

This document presents the opinion adopted by the BPC.

Process for the adoption of the opinion

ECHA received a request from the Commission on 3 August 2022. ECHA acts as the rapporteur in this type of procedures as agreed at BPC-3. The rapporteur presented the draft opinion to the BPC-45 meeting of 22-24 November 2022. Following the adoption of the opinion at BPC-45, the opinion was amended according to the outcome of the discussion.

Adoption of the opinion

Rapporteur: European Chemicals Agency (ECHA)

The BPC opinion was reached on 23 November 2022.

The BPC opinion was adopted by consensus. The opinion is published on the ECHA website at https://echa.europa.eu/bpc-opinions-on-article-38.

Further details of the opinion and background

1. Request for the opinion

Article 38 of Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (the "BPR") establishes that, if so requested by the Commission, pursuant to Article 36(2) or Article 37(2) of the BPR, the Agency shall issue an opinion within 120 days from the date on which the question was referred to it.

On 3 August 2022, ECHA received a request for a BPC opinion from the Commission to address questions relative to an unresolved objection during a mutual recognition procedure of the product "BOMBEX® PEBBYS® CS" related to the product being based on a wall encapsulation process by polymerization, involving isocyanate monomers or prepolymers, but no analysis carried out for the presence of isocyanates or free aromatic amines formed by hydrolysis.

The Commission has requested ECHA to formulate an opinion via the BPC on the following questions in order to decide on the authorisation of the product.

Regarding the potential presence of impurities stemming from the encapsulation process:

1. *Are free aromatic isocyanates present in the biocidal product BOMBEX® PEBBYS® CS?*
    - *In this context, ECHA is requested to determine whether the data from read-across provided by the applicant for a similar product is acceptable, considering that the isocyanates used in that particular product had a different structure than the isocyanates used in the product BOMBEX® PEBBYS® CS.*
2. *Are free aromatic amines formed during the encapsulation process and present in the biocidal product BOMBEX® PEBBYS® CS?*
3. *If free aromatic isocyanates and/or free aromatic amines are present in the biocidal product BOMBEX® PEBBYS® CS, can a risk be excluded for human health using the Threshold of Toxicological Concern (TTC) approach, meaning that the product meets the conditions in Article 19(1)(iii)?*
4. *If free aromatic isocyanates and/or free aromatic amines are present in the biocidal product BOMBEX® PEBBYS® CS, can a risk be excluded for the environment, meaning that the product meets the conditions in Article 19(1)(iv)?*

The Commission further indicated that, when addressing the above-mentioned questions, the following elements should be taken into account by the BPC:

(a) The product assessment report (PAR) of the biocidal product BOMBEX® PEBBYS® CS;

(b) Additional information provided by the applicant during the referral of the biocidal product BOMBEX® PEBBYS® CS, including read-across for a similar product that used isocyanates that had a different structure.

If considered necessary, ECHA could request the applicant to generate further analytical data.

2. Background

Biocidal product “BOMBEX® PEBBYS® CS” was authorised by Netherlands (reference Member State (rMS)) under the National authorisation procedure in accordance with Article 30 and 34(7) of the BPR. It is an insecticide (PT 18) which may be used to treat wasp/hornet nests outdoors.

BOMBEX® PEBBYS® CS is a capsule suspension product. The encapsulation process involves aromatic isocyanates, in the presence of water.

The referral of the disagreement on the evaluation of the product “BOMBEX® PEBBYS® CS” was submitted on 15 December 2020 by the icMSs (initiating concerned Member States) to the Coordiantion Group (CG), in accordance with Article 35(2) of the BPR. The referral was discussed during a teleconference on 28 January 2021 and the CG-45 meeting. During the discussions, one point of disagreement was resolved, while the other two remained unresolved. One of the unresolved disagreement points is related to the product containing a co-formulant including PBT/vPvB substances. Another unresolved point of disagreement is related to the product being based on a wall encapsulation process by polymerization, involving isocyanate monomers or prepolymers, but no analysis carried out for the presence of free aromatic amines formed by hydrolysis. As the CG did not reach a consensus agreement for the above mentioned two disagreement points, the rMS referred the unresolved objection to the Commission in accordance with Article 36(1) of the BPR.

The Commission only requested ECHA to formulate an opinion via the BPC on the unresolved disagreement point related to the product being based on a wall encapsulation process by polymerization, involving isocyanate monomers or prepolymers, but no analysis carried out for the presence of isocyanates or free aromatic amines formed by hydrolysis. This was due to the fact that the matter of a product containing a co-formulant including PBT/vPvB substances had already been resolved with a Commission Implementing Decision in relation to another product.

The icMS France considered that

- free aromatic amines formed during the encapsulation process by hydrolysis of isocyanates might be present in the final product,
- as well as residual aromatic isocyanates,
- therefore the potential presence of free aromatic amines and residual aromatic isocyanates should be analysed and requested as a post-authorisation condition.

During the referral discussions the manufacturer and the rMS brought clarifications on the encapsulation process, including evidence that for a similar product (for which the encapsulation process involves a different isocyanate) the level of free isocyanates could be measured and was 0.01% w/w [1]. The measured isocyanate was m-tetramethylxylylene diisocyanate (CAS number 2778-42-9, m-TMXDI), which was reported to be less reactive than 2,4-/2,6-toluene di-isocyanate (TDI) and present in a higher amount and therefore considered to be the worst case and expected to show higher residues of free isocyanate. In a read-across argument it was deducted that the remaining TDI content should be even lower than 0.01 % w/w. There were no direct measurements.

These clarifications and evidence did not convince the icMS France, who considered that the read-across provided by the applicant from a similar product was not acceptable, as the isocyanates used in that product had a different structure than those used in the

manufacturing process of the product “BOMBEX® PEBBYS® CS”. France also pointed out that the clarifications brought did not bring any information on the potential presence of free aromatic amines.

3. Answers to the questions from the Commission

The opinion of the BPC has considered the background information provided by the Commission in the opinion request, the Product Assessment Report (PAR) of the product in question, the information and comments provided by the applicant on request of ECHA and the conclusion reached during the Working Group (Human Health, Environment, Analytical Methods and Physico Chemical Properties WG) meeting that took place from 6 to 16 September 2022 (WG III 2022).

Question 1. *Are free aromatic isocyanates present in the biocidal product BOMBEX® PEBBYS® CS?*

- *ECHA is also requested to determine whether the read-across provided by the applicant for a similar product is acceptable, considering that the isocyanates used in that particular product had a different structure than the isocyanates used in the product BOMBEX® PEBBYS® CS.*

It is known from literature [2] that aliphatic isocyanates (like TMXDI) are less reactive than aromatic isocyanates and that sterical hinderance (as represented by the two neighbouring methyl groups in TMXDI) is reducing the reactivity of isocyanates. Both factors support the assumption that TMXDI is less reactive than TDI.

Based on these reactivity considerations, it can be concluded that the read-across to TMXDI will result in a conservative estimate for the presence of free isocyanates in BOMBEX® PEBBYS® CS. Therefore the measured values for TMXDI (0.01% w/w) can be used also as a worst case estimate for TDI present in BOMBEX® PEBBYS® CS.

The hydrolysis reaction of TDI and pMDI in pure water has been studied in detail [3] and the rate of reaction depends heavily on the surface area of the isocyanate in the heterogeneous reaction, i.e. mostly the stirring speed, and on the total loading with isocyanate. Under well stirred and not catalysed conditions in pure water, half-lives of TDI at 1 % w/w of less than 1 h were observed. The observed half-life for pMDI was much longer (around 20 h) due to high viscosity and less efficient dispersion by stirring.

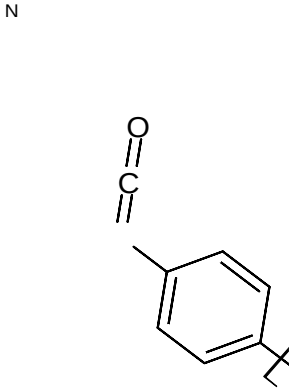
Considering these measured half-lifes and the fact that the encapsulation reaction makes use of catalysts and an organic solvent to dissolve the isocyanates, it can be reasonably presumed that in the aqueous solution the degradation of free isocynates will be fast enough to exclude their presence after a few days.

It is therefore concluded that the read-across was acceptable and additionally that the presence of free isocyanates in the aqueous phase can be excluded after a few days of storage.

Question 2. *Are free aromatic amines formed during the encapsulation process and likely to be present in the biocidal product BOMBEX® PEBBYS® CS?*

Based on mechanistic considerations delivered by the applicant and known from literature it can be concluded that free aromatic amines are an important intermediate product in the reaction. (see Annex 1 Formation of the microcapsules).

Table 1 Free aromatic amines potentially present in the biocidal product BOMBEX® PEBBYS® CS.

isocyanate	Structure of isocyanate	Structure of corresponding aromatic amine	Aromatic amine
TDI 2,4-/2,6-toluene di-isocyanate 247-722-4 26471-62-5 The substances is an 80:20 mixture of the 2,4 and 2,6 isomers [2]			TDA 4-methyl-m-phenylenediamine 95-80-7
pMDI Diphenylmethane diisocyanate oligomer 9016-87-9 This substance contains 40 to 60% 4,4'-Methylenediphenyl diisocyanate (4,4'-MDI) [2]			AFAFC - amine functional aniline formaldehyde condensate; Formaldehyde, oligomeric reaction products with aniline
MDI 4,4'-Methylenediphenyl diisocyanate 101-68-8			MDA; 4,4'-methylenedianiline

The formation of free aromatic amines and the subsequent polymerisation reaction take place at the water/organic solvent interface. The intermediate free aromatic amines may have the possibility to diffuse into the aqueous phase and remain unreacted. The proportion of free amines that may stay unreacted depends on the specific reaction conditions: total exposed surface area, reaction kinetics of the amine formation and amine consumption reactions, temperature, pH, etc

From these considerations it can be concluded **free aromatic amines are formed during the reaction** and that **the presence of free aromatic amines after the reaction cannot be excluded** based on available data.

Estimation of expected concentrations

To make an attempt at estimating the possible risks of free aromatic amines, a rough estimation of the expected concentration levels was performed. This estimation is primarily based on experimental data on the hydrolysis reaction of TDI and pMDI in pure water [3]. For hydrolysis of TDI, a level of 27 mg/L (≈ 0.0027 % w/w; ≈ 27 ppm; about 0.4 % yield of initial TDI) was measured with a loading of 10 g/L TDI. For pMDI, a smaller amount of the corresponding free amine was found, but this is likely due to less efficient dispersion of pMDI because of its high viscosity. The results of the study for TDI are summarised in Figure 1.

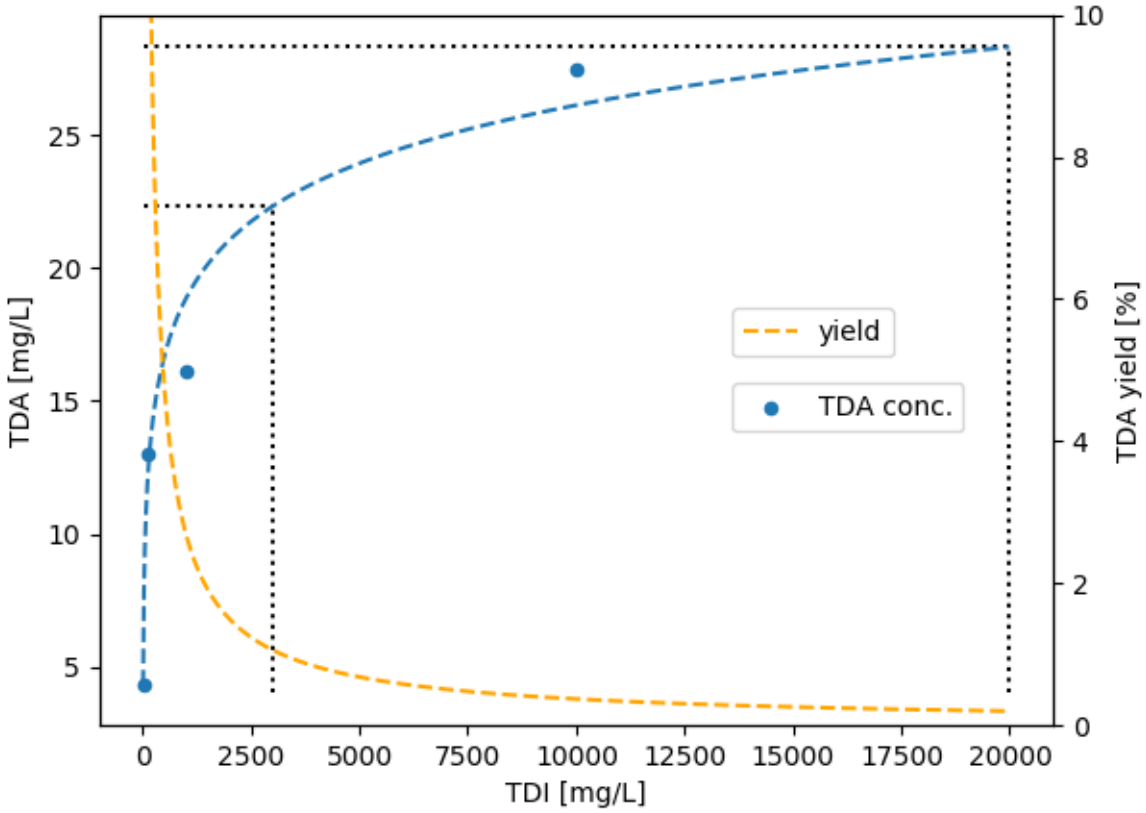


Figure 1 water hydrolysis of TDI according to [3]

For this estimation it is assumed that MDI (about 40-60% of pMDI) behaves essentially identically to TDI as they are similar in reactivity, present in the same droplets with identical viscosity and surface area and have similar molecular mass leading to similar diffusion behaviour. The remaining polymeric part of pMDI may have deviating behaviour, but as worst case estimate it is assumed to also behave identically to TDI. With this assumption, a free amine concentration can be estimated from the data for TDI by extrapolation in Figure 1. Starting with an isocyanate loading of 2% (≈20000 mg/L) an approximate concentration of 30 mg/L (≈0.0030 %) of free amine is estimated. This value is connected to major uncertainties regarding esp. the comparability of experimental conditions like surface area and pH.

The solubility of TDA depends heavily on the pH value of the aqueous phase (see Figure 2). The solubility is roughly constant for neutral and basic aqueous solutions but at lower pH values , there is a dramatic increase of solubility by a factor of 100 between pH 7 and pH 4. As there is an acidic pH regulator in the aqueous phase of the product [4], it seems possible that higher levels of free amine could be reached.

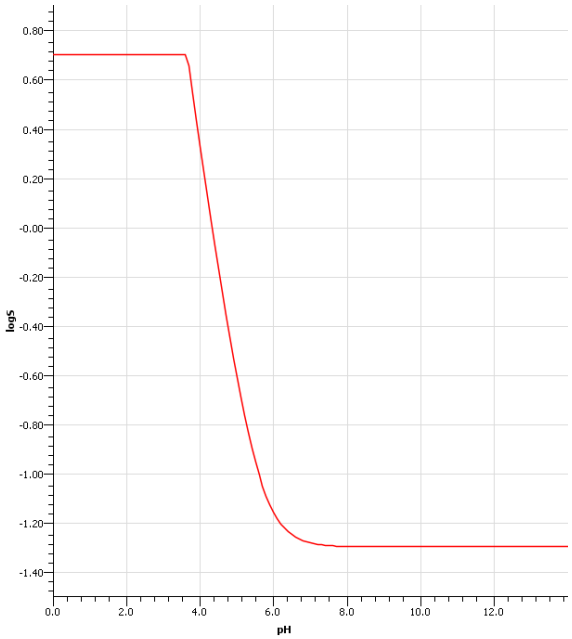


Figure 2 predicted solubility (logS) of TDA by ChemAxon Solubility Predictor

To account for these unknown variations, a factor of 10^2 is proposed, leading to an **estimated amount of free aromatic amines of 0.3 % w/w** (3000 mg/L). This is expected to be a worst case estimate as the total amount of isocyanates present is only 2% w/w so that the estimate corresponds to more than 20% of maximally possible free aromatic amine considering the molecular weight. It is expected that the percentage consumed in the micro capsule formation is higher than 80%.

Levels of individual free aromatic amines can also be estimated by considering their relative proportion of the corresponding isocyanates in the starting material, but these values are linked to even higher uncertainties and should be used with caution.

The free amines expected to be present are listed in Table 1 and their worst case estimated levels in the biocidal product “BOMBEX® PEBBYS® CS” are provided in Table 2 .

Table 2 rough estimates of individual free aromatic amines

	% w/w of isocyanate	Estimated individual concentration	Estimated total concentration
TDA	0.3	0.3/2.1*0.3=0.044%	0.3%
AFAFC	1.8	1.8/2.1*0.3=0.256%	
MDA	Ca. 0.9 (part of pMDI)	0.9/2.1*0.3=0.128% (part of AFAFC)	

Question 3. *If free aromatic isocyanates and/or free aromatic amines are present in the biocidal product BOMBEX® PEBBYS® CS, can a risk be excluded for human health using the Threshold of Toxicological Concern (TTC) approach, meaning that the product meets the conditions in Article 19(1)(iii)?*

Free isocyanate impurities

The presence of free isocyanates in the biocidal product BOMBEX® PEBBYS® CS can be excluded (see Question 1). Therefore, no risk is foreseen for human health related to these substances.

Free aromatic amine impurities

Based on available data, the presence of free aromatic amines in the biocidal product BOMBEX® PEBBYS® CS cannot be excluded (see Question 2).

A worst case estimated level of 0.3% w/w of aromatic amines was determined to be possibly present in the biocidal product BOMBEX® PEBBYS® CS (Table 2). The classification and labelling (C&L) information on the aromatic amine substances that are suspected to be present in BOMBEX® PEBBYS® CS was extracted from ECHA's dissemination website and is provided in Table 3. All of them are classified (or notified) as genotoxic carcinogens.

Table 3 Classification of free aromatic amines potentially present in the biocidal product BOMBEX® PEBBYS® CS.

Name	EC No.	CAS No.	Estimated worst case concentration in BOMBEX® PEBBYS® CS	Classification & labelling (for HH endpoints)
TDA; 4-methyl-m-phenylenediamine	202-453-1	95-80-7	0.044%	Harmonized classification Acute Tox. 3*, H301 Acute Tox. 4* , H312 Skin Sens. 1, H317 Muta. 2, H341 Carc. 1B, H350 STOT RE 2 *, H373 ** Repr. 2, H361f *** C&L Inventory (europa.eu)
AFAFC - amine functional aniline formaldehyde condensate; Formaldehyde, oligomeric reaction products with aniline (amine corresponding to PMDI)	500-036-1	25214-70-4	0.256%	Notified classification (majoritary): Skin Sens. 1, H317 Muta. 2, H341 Carc. 1B, H350 STOT SE 1, H370 STOT RE 2, H373 C&L Inventory (europa.eu)
MDA; 4,4'-methylenedianiline	202-974-4	101-77-9	0.128%	Harmonized classification: Skin Sens. 1, H317 Muta. 2, H341 Carc. 1B, H350 STOT SE 1, H370 ** STOT RE 2 *, H373 ** C&L Inventory (europa.eu)

* The "*" indicates that manufacturers or importers must apply at least this minimum classification, but must classify in a more severe hazard category in the event that further information is available which shows that the hazard(s) meet the criteria for classification in the more severe category (see Annex VI, Section 1.2.1 of the CLP Regulation).

** The classification under 67/548/EEC indicating the route of exposure has been translated into the corresponding class and category according to this Regulation but with a general hazard statement not specifying the route of exposure as the necessary information is not available.

*** In order not to lose information from the harmonised classification for fertility and developmental effects under Directive 67/548/EEC, the classifications have been translated only for those effects classified under that Directive.

In addressing Question 3, it should be highlighted that there is no guidance specifically addressing the situation/issue of the human health assessment of impurities in biocidal products.

Two possible approaches to address the question were discussed in HH WG-III-2022 and are presented below. Each approach has advantages/disadvantages but reach the same conclusions.

Approach I: Determining the level at which an impurity affects the toxicity of the product

In order to assess whether a risk can be excluded for human health due to the potential presence of these free aromatic amines in the biocidal product BOMBEX® PEBBYS® CS, a risk assessment was performed using the Threshold of Toxicological Concern (TTC) and approach described in the Technical Equivalence (TE) guidance [5] (see section 6.3.3.1. *Assessment of change in toxicity*). The TE guidance provides:

> *For each endpoint, the AS-alternative should not have more than a 2-fold difference in the NOAEL compared to the corresponding NOAEL or other value used for deriving reference values in the AS-reference […]*
>
> *If the endpoint and/or the effects are different (and not additive or synergistic), the following equation can be used to calculate whether an impurity may significantly affect the overall (lowest) NOAEL of the AS-alternative:*
>
> *Percentage of impurity that would not significantly affect the NOAEL of the active substance = [$NOAEL_{impurity}$ / $NOAEL_{active\ substance}$] × 100*
>
> *The above equation indicates whether there would be a possible impact on the NOAEL of the active substance due to the presence of the impurity i.e. a percentage of impurity that would affect the NOAEL of the active substance. The value obtained can be used in comparison whether the impurity (at the certain concentration) would increase more than 2-fold the toxicity of the active substance.*

The same principles apply for each of the three impurities since they are all genotoxic carcinogens. The level of impurity not impacting the toxicity of the product BOMBEX® PEBBYS® CS should be calculated.

Since the substances are genotoxic carcinogens without reference values (see TDA evaluation [6], MDA evaluation [7]), the Threshold of Toxicological Concern (TTC) [8,9] for genotoxic carcinogens can be used, i.e. 0.0000025 mg/kg bw/d. This value would represent the level of acceptable exposure when applying the TTC concept, representing a value at which a genotoxic carcinogen would be estimated to cause an increase in cancer incidence of one in a million in the human population.

To find the acceptable % of each genotoxic carcinogen impurity, this TTC value is compared with the AEL of the AS permethrin, using the following adjusted equation from the Technical Equivalence guidance:

$$\%\ \text{of impurity that would not significantly affect the AEL of the AS} = [TTC_{impurity} / AEL_{AS}] \times 100\%$$

The document agreed at BPC-31 *Interpreting the definition of relevant impurities* [10] indicates that the most appropriate reference value should be selected based on expert judgement, while also indicating that the highest AEL should be selected.

The Human Health Working Group (HH WG-III-2022) supported using the AEL_{acute} (0.5 mg/kg bw/day) [11] in the assessment noting that: (i) genotoxicity is not only a long term effect; (ii) in an earlier case, the highest reference value was used for genotoxic carcinogenicity; (iii) using the AEL_{acute} is worst-case and leads to the most conservative assessment.

Using the equation from the TE guidance (above), the percentage of acceptable genotoxic carcinogen impurity as % of the AEL of the active substance is:

$= [TTC_{impurity} / AEL_{active\ substance}] \times 100\%$
$= [0.0000025/0.5] \times 100\%$
$= 0.0005\%$

The Human Health Working Group (HH WG-III-2022) considered it unnecessary to adjust the % of acceptable genotoxic impurities to the concentration of permethrin AS in the product since the free aromatic amines are not impurities of the AS and the product should be considered as a whole.

Applying the TTC concept and considering that the genotoxic carcinogen impurity is part of the product, **the acceptable percentage of genotoxic carcinogen impurity in the product is 0.0005%**

This is well below the estimated worst case concentrations, as indicated in Table 4 below.

Furthermore, it would not be appropriate to consider the genotoxic carcinogens only on an individual basis, but they should be considered together.

See Table 4 for an overview of the outcome of the assessment.

Table 4 Outcome of the HH assessment of the impact of the levels of free aromatic amines potentially present in the biocidal product BOMBEX® PEBBYS® CS.

	Acceptable impurity level not impacting the toxicity of BOMBEX® PEBBYS® CS	**Estimated worst case impurity concentration in BOMBEX® PEBBYS® CS**	**Outcome of assessment**
TDA; 4-methyl-m-phenylenediamine	0.0005%	0.044%	The worst case TDA level estimation is 88 × higher than the acceptable level.
AFAFC - amine functional aniline formaldehyde condensate; Formaldehyde, oligomeric reaction products with aniline (amine corresponding to PMDI)	0.0005%	0.256%	The worst case AFAFC level estimation is 512 × higher than the acceptable level.
MDA; 4,4'-methylenedianiline	0.0005%	0.128%	The worst case MDA level estimation is 256 × higher than the acceptable level.

	Acceptable impurity level not impacting the toxicity of BOMBEX® PEBBYS® CS	Estimated worst case impurity concentration in BOMBEX® PEBBYS® CS	Outcome of assessment
Total of aromatic amines	0.0005%	0.3%	The worst case aromatic amines level estimation is 600 × higher than the acceptable level.

In light of this assessment, a risk for human health due to the possible presence of free aromatic amines in the biocidal product BOMBEX® PEBBYS® CS cannot be excluded using the Threshold of Toxicological Concern (TTC) concept.

Comparison with AEL is considered appropriate as it is a stable, agreed value for the permitted exposure to the AS, and as such provides an assessment that is independent of the product and use. The approach is also pragmatic as no exposure assessment is needed. It is however a new approach since impurities are normally considered in the AS and not in the product, and there is no guidance for such an assessment.

Approach II: considering the free aromatic amine impurities as SoC

In the context of the e-consultation, an alternative approach was proposed where it was argued that free aromatic amines could also be viewed as Substances of Concern (SoCs) as they are not part of the active substance, but rather are introduced during the manufacturing process of the encapsulated product. An example SoC assessment was provided and discussed at the Human Health Working Group (HH WG-III-2022) (see Annex 2 for details).

Briefly, a quantitative risk assessment was performed for one of the aromatic amine impurities following the SoC guidance in Annex A of the Guidance on BPR: Volume III Parts B+C [12]. In the absence of specific reference value, the TTC value for genotoxic substances was used (0.0000025 mg/kg bw/d). The estimated exposure of the aromatic amine impurities was compared to this TTC value. As an example, the dermal exposure of a toddler to the aromatic amine impurity AFAC in scenario 6 [Dermal contact with treated surfaces] of the PAR was calculated using ConsExpo, and then compared with the TTC. The dermal exposure of a toddler was 152 × higher than the TTC value. Considering this high exceedance and the use patterns of the product, an exceedance of the corresponding TTC value for other scenarios and amines and the sum of all relevant amines is also expected.

In summary, using approach II a risk for human health due to the possible presence of free aromatic amines in the biocidal product BOMBEX® PEBBYS® CS cannot be excluded.

An advantage of Approach II is that SoCs are defined in the BPR while impurities in a product would be a new concept. A disadvantage is that the assessment is more complex since an exposure assessment is needed, in principle for each use separately.

This alternative approach was considered useful to complement the assessment, to cover possible situations where a risk would be identified using Approach I while no exposure would be occurring during product use. Although this consideration is not relevant in this specific case, using both approaches could be useful in assessing other dossiers to check if a risk is also identified considering exposure.

Uncertainties and additional considerations

- The estimations of the levels of free aromatic amines are based on worst case calculations. Noting the reactivity of these species and the impact of different parameters (e.g. temperature) and processes on their levels in the product, these estimations may be too conservative.

- In order to correctly classify the product using the relevant calculation methods from the CLP Regulation (EC) No 1272/2008, the complete quantitative composition of the product should be available (See Annex III, Title 1, Section 2 of the BPR). The classification of a product according to the CLP based on the hazardous properties of its ingredients requires valid data on each of the components (See Annex III, Title 1, Section 8 of BPR). Worst-case concentration estimates of the ingredients cannot be used for the classification of biocidal products; measurements and quantification of the impurities would be needed.

- Applying the principles from the CLP and Generic Concentration Limit (GCL) for Carcinogens Cat. 1B (i.e. 0.1%) [13], the presence of 0.3% of aromatic amine impurities that are genotoxic carcinogens in BOMBEX® PEBBYS® CS would suggest product classification as Carcinogen Cat 1B. Such classification would have major impact on the uses and outcome of the risk characterisation. According to the current PAR[1], the product is applied by spraying by professionals and trained professional users. If the product would be classified as Carcinogen Cat 1B, in accordance with the CLP Guidance on Labelling and Packaging [14] (p. 164-5) additional PPE/RPE would be needed (eye protection/face protection) and special instructions for use should be set which might restrict the application to methods with low exposure potential, excluding spraying.

- The considerations above on carcinogenicity would be subject to a different assessment with additional data from the applicant. A worst case human health risk assessment using the TTC should be regarded as a first step to evaluate whether a risk for human health can be excluded. As this is not the case based on currently available information, a refinement of the human health risk assessment would be needed using substance specific data, exposure assessments and a risk assessment methodology applicable for genotoxic carcinogens (e.g. 'linearised' approach referring to the lifetime cancer risk or the 'Large Assessment Factor' approach – see 2.4.1.1 of BPR guidance Parts B+C [12]).

In conclusion, with the currently available information a risk for human health cannot be excluded using the Threshold of Toxicological Concern (TTC) concept, meaning that the conditions in Article 19(1)(iii) of the BPR are not met.

Question 4. *If free aromatic isocyanates and/or free aromatic amines are present in the biocidal product BOMBEX® PEBBYS® CS, can a risk be excluded for the environment, meaning that the product meets the conditions in Article 19(1)(iv)?*

The concern regarding the free aromatic isocyanates and/or free aromatic amines is that they are considered to be genotoxic carcinogens. Currently, the genotoxic properties of a substance are not considered for the environmental risk assessment. This is because neither a qualitative nor quantitative approach as applied in the human health risk assessment for

[1] R4BP 3 case: https://r4bp-main.echa.europa.eu/r4bp-web-authority/asset/na.xhtml?id=NL-0016408-0000
"Workers need to wear gloves and coveralls when the product is applied by medium pressure spraying (i.e. at 4 to 7 bar pressure) and low-pressure spraying (i.e. at 1 to 3 bar pressure).
The professional user needs to wear gloves during application by trigger spray."

genotoxic carcinogens is practicable in the environmental risk assessment. Endpoints like tumour incidence rates and subsequent cancer risks are related to individual risks in humans, which in most cases are difficult to link those effects to populations. However, as mentioned in the Guidance on BPR: Vol IV Environment Parts B+C [12], *it is not unlikely that the conservative approach followed in the risk assessment for man indirectly exposed via the environment for genotoxic substances, will also be protective for individual top predators*. Therefore, the assumption is that if Article 19(1)(iii) is fulfilled, Article 19(1)(iv) of the BPR is fulfilled as well (refer to question 3).

Overall conclusion

It is concluded that the read-across from a similar product was acceptable and additionally that the presence of free isocyanates in the aqueous phase can be excluded after a few days of storage.

It is concluded that free aromatic amines are formed during the reaction and that the presence of free aromatic amines after the reaction cannot be excluded based on available data

With the currently available information, a risk for human health cannot be excluded using the worst case concentration estimates for free aromatic amines and the Threshold of Toxicological Concern (TTC) concept, meaning that the product does not meet the conditions in Article 19(1)(iii) of the BPR.

Currently, the genotoxic properties of active and non-active substances in biocidal products are not considered for the environmental risk assessment. However, the assumption is that if Article 19(1)(iii) is fulfilled, Article 19(1)(iv) of the BPR is fulfilled as well. Here it was concluded that Article 19(1)(iii) is not fulfilled meaning that the product cannot be concluded to meet the conditions in Article 19(1)(iv) of the BPR.

References

1. Eurofins Biolab. Validation of a GC method for the identificaiton and the quantificatin of the impurity 1,3-bis(isocyanato-1-methylethyl)benzene (TMXDI) in the test item "Bombex Farumy". ; 2018.

2. Six C, Richter F. Isocyanates, Organic. In Ullmann's Encyclopedia of Industrial Chemistry.; 2003.

3. Yakabe Y, Henderson KM, Thompson WC, D. P, Tury B, Bailey RE. Fate of Methylenediphenyl Diisocyanate and Toluene Diisocyanate in the Aquatic Environment. Environ. Sci. Technol. 1999; 33(15): p. 2579-2583.

4. GAT microencapsulation. description_production_statement_triethylamin_permethrin.pdf. ; 2016 November.

5. European Chemicals Agency. Guidance on the Biocidal Products Regulation: Volume V Guidance on applications for technical equivalence. Helsinki; 2018 [cited 2022 October]. Available from: https://echa.europa.eu/documents/10162/2324906/guidance_applications_technical_equivalence_en.pdf/18f72d37-98b6-47c8-98bb-941afeff6968.

6. European Communities. 4-METHYL-M-PHENYLENEDIAMINE (TOLUENE-2,4-DIAMINE) SUMMARY RISK ASSESSMENT REPORT.; 2008 [cited 2022 October]. Available from: https://echa.europa.eu/documents/10162/a306907a-8401-4a75-8a84-88b9f225d5cf.

7. European Communities. European Union Risk Assessment Report 4,4'-methylenedianiline.; 2001 [cited 2022 October]. Available from: https://echa.europa.eu/documents/10162/ba567fa3-282c-4b37-bcba-f82fd9ae52bc.

8. European Food Safety Authority and World Health Organization. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree.; 2016 [cited 2022 October]. Available from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2016.EN-1006.

9. EFSA Scientific Committee. Guidance on the use of the Threshold of ToxicologicalConcern approach in food safety assessment.; 2019 [cited 2022 October]. Available from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5708.

10. Biocidal Product Committee. Interpreting the definition of relevant impurities. Helsinki; 2020 [cited 2022 October]. Available from: https://webgate.ec.europa.eu/s-circabc/d/a/workspace/SpacesStore/00f7cfb3-9339-413e-b5d9-37cf01bfb5df/BPC-31_relevant%20impurities_final.docx.

11. Department of Agriculture, Food and the Marine, Ireland. Evaluation of active substances Assessment Report Permethrin Product-Type 18. Helsinki; 2014 [cited 2022 October]. Available from: https://echa.europa.eu/documents/10162/ff18b40c-e4f6-469e-377d-6e5aca835bd2.

12. European Chemicals Agency. Guidance on the BPR: Volume III Human Health, Assessment & Evaluation (Parts B+C). Helsinki; 2017 [cited 2022 October]. Available from: https://echa.europa.eu/documents/10162/2324906/biocides_guidance_human_health_ra_iii_part_bc_en.pdf/30d53d7d-9723-7db4-357a-ca68739f5094.

13. European Chemicals Agency. Guidance on the Application of the CLP. Helsinki; 2017 [cited 2022 October]. Available from: https://echa.europa.eu/documents/10162/2324906/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5?t=1499091929578.

14. European Chemicals Agency. Guidance on labelling and packaging in accordance with Regulation (EC) No. Helsinki; 2021 [cited 2022 October]. Available from: https://echa.europa.eu/documents/10162/23036412/clp_labelling_en.pdf/89628d94-573a-4024-86cc-0b4052a74d65.

15. Blank WJ, He AZ, Hessell ET. Catalysis of the isocyanate-hydroxyl reaction by non-tin catalysts. Progress in Organic Coating. 1999; 35(1-4): p. 19-29.

16. Jesmond Bioscience. DETAILS ON THE POLYMERIZATION REACTIONS..

Annexes

Annex 1. Formation of the microcapsules

As reported in the dossier

In the dossier, there is a description of the encapsulation process provided in the document "description_production_statement_triethylamin_permethrin.pdf" [4].

The process involves two isocyanates, a cross linker and a catalyst.

ingredient	Function	Concentration [% w/w]
Ongronat 1080 2,4-/2,6-toluene di-isocyanate 247-722-4 26471-62-5	Wall forming isocyanate	0.3%
Desmodur 44V20L Diphenylmethane diisocyanate oligomer 9016-87-9	Wall forming isocyanate	1.8 %
Tetrakis Tetramethoxymethyl glycoluril 17464-88-9	Wall forming cross linker	0.3 %
Triethylamine 121-44-8 204-469-4	catalyst	0.024

There is a detailed flow chart describing the process flow. In short, isocyanates and crosslinker are mixed into an organic phase, which is then mixed with a solution of the catalyst before being combined with an aqueous phase to form an emulsion. On the droplet interface in the emulsion a polyurea film is formed.

The amount of triethylamine after the reaction was determined to be below the limit of quantitation (0.01 % w/w).

As reported in the PAR

In the confidential annex to the PAR, the poly urea wall is described to be produced from the following material:

Common name	IUPAC name	Function	CAS number	EC number	Content (%
Ongronat 1080	m-tolylidene diisocyanate (TDI)	Capsule wall precursor	Not	247-722-4	0.30

Common name	IUPAC name	Function	CAS number	EC number	Content (%
			available		
Desmodur 44V20L	diphenylmethane-diisocyanate, isomers and homologues	Capsule wall precursor	9016-87-9	Not available	1.80
Tetrakis	Tetrakis(triphenylphosphine)-palladium (0)	Capsule wall precursor	14221-01-3	238-086-9	0.30
Triethylamine	Triethylamine	Capsule wall precursor	121-44-8	204-469-4	0.024

The given composition lists another related substance:

Dibutylin Dilaurate for synthesis	Dibutyltin dilaurate	Catalyst	77-58-7	n.a.	0.01

This substance is a common catalyst used for the reaction of isocyanates with hydroxy groups (including water) [15].

Note the likely incorrect identification of “Tetrakis” and the likely incorrect function reported for triethylamine.

As reported in additional information

In additional information provided by the commission together with the mandate for this opinion, the manufacturing of the microcapsules is further described [16]. Here it is clarified that the initial reaction is the formation of amines from the reaction of isocyanate with water at the interface between organic solvent and water at the droplet surface. The intermediately formed amines react with available further isocyanate to form a urea bond. The forming polyurea is crosslinked via a butylated glycoluril-formaldehyde resin. The crosslinking is reported to form a new amine from a reacting isocyanate group bond replacing a butyloxy group with release of carbondioxide.

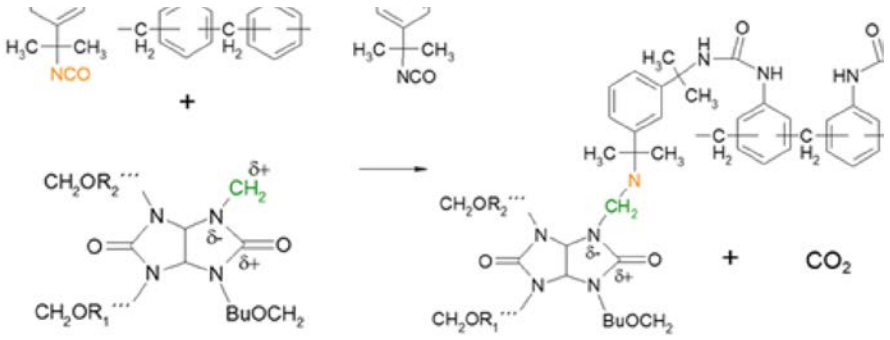


Figure 3 reaction of the cross linker

Note that the reported reactants in this document are

- **TMXDI®** (m-Tetrametylxylene diisocyanate; CAS No. 27778-41-8) which is an aliphatic isocyanate and less reactive with the NCO content of ~ 34.4%;
- **ONGRONAT 2100** (Polymethylene polyphenyl poliisocyanate; CAS No. 9016-87-9) which is a pre-polymeric aromatic isocyanate and very reactive

,from which TMXDI is significantly different from the material used for the product Bombex Pebby CS.Note also that the company is not the same as reported previously.

Overall picture

It seems reasonable to conclude from the available information that the encapsulation process is performed with the following conditions:

- All isocyanates and the crosslinker are pre-mixed into an organic solvent
- The catalyst solution is added to the organic phase just before emulsion formation
- The organic phase is dispersed into the aqueous phase to form an emulsion
- The polymerisation starts at the oil/water interface by amine formation from isocyanate (with generation of carbon dioxide)
- Crosslinking is performed without the involvement of intermediate free amines
- Polymerisation does involve the presence of free amines as intermediate products

Material used for encapsulation:

ingredient	Function	Concentration [% w/w]
TDI Ongronat 1080 2,4-/2,6-toluene di-isocyanate 247-722-4 26471-62-5 The substances is an 80:20 mixture of the 2,4 and 2,6 isomers [2]	Wall forming isocyanate	0.3%
pMDI Desmodur 44V20L Diphenylmethane diisocyanate oligomer 9016-87-9 This substance contains 40 to 60% 4,4'-Methylenediphenyl diisocyanate (4,4'-MDI) [2].	Wall forming isocyanate	1.8 %
Tetrakis Tetramethoxymethylglycoluril	Wall forming cross linker	0.3 %

ingredient	Function	Concentration [% w/w]
17464-88-9		
Triethylamine 121-44-8 204-469-4	catalyst	0.024
Dibutyltin dilaurate 77-58-7 201-039-8	catalyst	0.01

Annex 2. SoC assessment and calculations

Using Approach II (see Question 3, Approach II: considering the free aromatic amine impurities as SoC), the assessment would be as follows:

For the amines AFAFC and MDA, the maximum concentration estimates are above 0.1 %. Since they are classified with Carc. 1B and the GCL is 0.1 %, this would lead to classification of the biocidal product with Carc. 1B, H350. Hence, a quantitative risk assessment as proposed in the guidance on the identification and evaluation of substances of concern (Annex A of the Guidance on BPR: Volume III Parts B+C) [12] would have to be performed.

This assessment should be done by comparing the estimated exposure with a reference value. In the absence of specific reference values and considering the mutagenic and carcinogenic properties of these components, the TTC value for genotoxic substances should be used.

As an example, scenario 6 of the PAR for a toddler exposed to the estimated maximum concentration of 0.00128 % AFAFC (dilution factor 200) was calculated using ConsExpo. Deviating from the corresponding active substance assessment in the draft PAR, a transfer coefficient of 0.2 m^2/h was used for a toddler of 10 kg. Dermal absorption was set to 50 % (default). All other parameters were adopted from the draft PAR.

The dermal exposure of a toddler in scenario 6 was estimated to be 0.00038 mg/kg bw/d. This corresponds to 15200 % of the TTC value of 0.0000025 mg/kg bw/d. Considering this high exceedance, an exceedance is expected of the corresponding TTC value for other scenarios and amines and the sum of all relevant amines.

```
Substance
Name       AFAFC
CASNumber
Molecular weight     222        g/mol
KOW        2,5         10Log
Product
Name       AFAFC
Weight fraction substance      0,256      % (concentrate)
Population
Name       Toddler
Body weight          10          kg
Scenario post application (child)
Frequency  126         per year
Description
Inhalation
Exposure model       n.a.
Absorption model     n.a.
Dermal
Exposure model       Direct contact - Rubbing off
Exposed area         3E+03       cm²
Weight fraction substance      0,00128     %
Transfer coefficient 0,2         m²/hr
Dislodgeable amount  3           g/m²
Contact time         60          minute
Contacted surface    22          m²
Absorption model     Fixed fraction
Absorption fraction  50          %
Oral
Exposure model       n.a.
Absorption model     n.a.
```

Results for scenario post application (child)
Dermal

Dermal load	2,56E-06	mg/cm²		
External event dose	0,000768	mg/kg bw		
External dose on day of exposure			0,000768	mg/kg bw
Internal event dose	0,000384	mg/kg bw		
Internal dose on day of exposure			0,000384	mg/kg bw/day
Internal year average dose		0,000133	mg/kg bw/day	

Integrated

Internal event dose	0,000384	mg/kg bw		
Internal dose on day of exposure			0,000384	mg/kg bw/day
Internal year average dose		0,000133	mg/kg bw/day	

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