Recommendation of the BPC Working Groups

In situ generated active substances – Risk assessment and implications on data requirements for active substances generated *in situ* and their precursors

Contents

1. Preface

This recommendation is a compilation of documents agreed by the four BPC working groups in 2016 and 2017.

The terminology and definitions (section 3) and details of the requirements with regard to identity, physical, chemical and physical hazard properties (section 4) were discussed and agreed by the Working Group - Analytical Methods and Physico-Chemical Properties at its meetings WG-III-2016, WG-IV-2016 and WG-III-2017.

The clarification on assessing efficacy of the in situ active substances (section 5) was agreed by the Efficacy WG at WG-V-2016.

The approach for human health risk assessment (section 6) was discussed in five Human Health WG meetings in 2016 and 2017. The final text was agreed at WG-III-2017.

The approach for environmental risk assessment (section 7) was discussed at the Environmental WG meetings WG-IV-2016, WG-V-2016, WG-II-2017 and WG-III-2017 where it was agreed.

2. Introduction

The regulatory status of *in situ* generated active substances and their precursors is summarised in the competent authority meeting document *CA-March15-Doc.5.1-Final*[1] (revised 23 June 2015) *Management of in situ generated active substances in the context of the Biocidal Products Regulation (BPR, Regulation (EU) No 528/2012)*.

According to this document, *in situ* generated active substances are defined as substances that are generated at the place of use from one or more precursor(s). The active substance is defined by reference to the precursor(s) and the substance generated.

According to the competent authority meeting document (*CA-Nov15-Doc.5.5 Final_Rev 1*[1]), only the properties of the *in situ* generated active substance are considered to define whether the exclusion, substitution and Annex I listing criteria are met during the approval process.

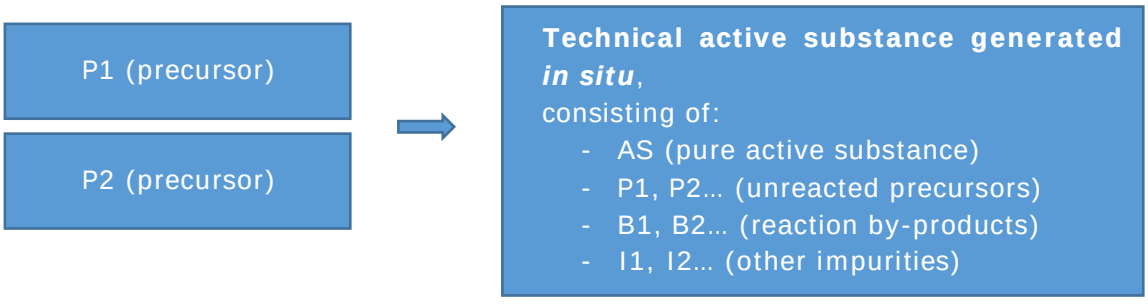
For *in situ* generated active substances, the **biocidal product** subject to authorisation is either 1) the substances and/or mixtures generating the active substance, or 2) the active substance generated from substances or mixtures that cannot themselves be authorised as biocidal products (e.g. ozone generated from ambient air, active chlorine generated from seawater).

While the information requirements for active substances apply to *in situ* generated active substances, the requirements for precursors have not been specified. This document intends to clarify the principles for information requirements and risk assessment of the precursors of *in situ* generated active substances but also sheds some light on the information requirements for the active substances generated *in situ*.

3. Terminology and definitions

The following *in situ* generation scheme illustrates the terminology:

Figure 1: *In situ* generation reaction scheme



[1] CA-Nov15-Doc.5.5 – Final_Rev1. Harmonised classification of in situ generated active substances. https://circabc.europa.eu/d/a/workspace/SpacesStore/d707228e-baa3-45d4-984c-29b2f47706ae/CA-Nov15-Doc.5.5%20-%20Final_rev1%20-%20Classification%20and%20in%20situ%20generated%20AS.doc

In situ generation means the reaction of one or more precursor(s) to generate the technical active substance at the place of use for direct application without isolation, purification, storage or transport.

Precursor (P) is a substance or mixture, from which an active substance (including free radicals) is generated *in situ*. Therefore, all substances that are actively involved in the generation process, as catalysts, acids etc., are regarded as precursors. A precursor may have a biocidal activity in its own right and/or react on its own or with other chemicals to form the *in situ* generated biocidal active substance. Unreacted precursors may be present as impurities in the composition of the technical active substance generated *in situ* unless they are fully consumed in the reaction. Active substance releasers are not precursors.

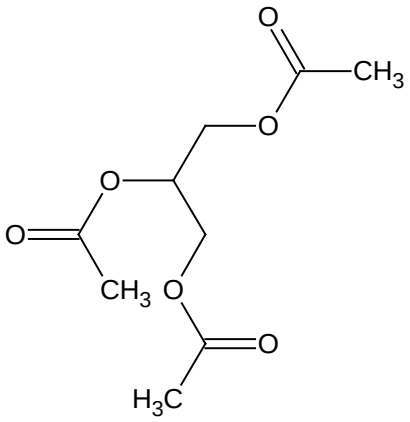
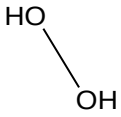
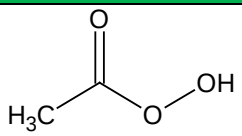
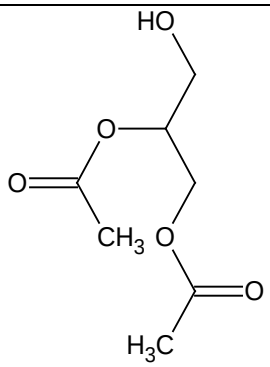
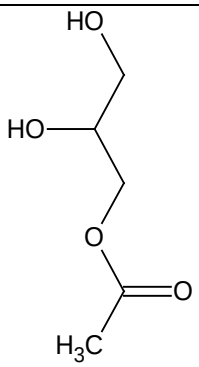
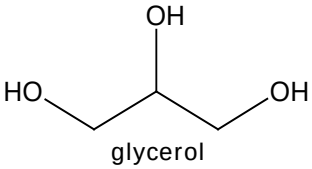
Technical active substance generated *in situ* comprises the pure active substance, reaction by-products, unreacted precursors and other impurities (e.g. contaminants from precursors).

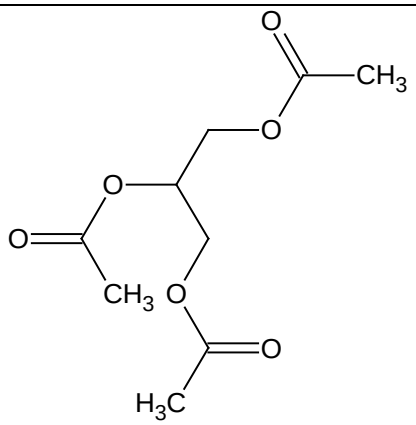
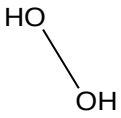
In situ generated active substance (AS) refers to the **pure** active substance generated, and does not include unreacted precursors, reaction by-products and impurities (e.g. contaminants from precursors). The pure active substance may consist of multiple active chemical species. If additives and/or unreacted precursors are active substances on their own right, these additives and/or unreacted precursors will be regarded as part of the pure active substance; in such cases unreacted precursors are not impurities.

Impurities (I) are the non-active part of the technical active substance generated *in situ*. They originate from the precursors or are the result of (unwanted) secondary or incomplete reactions during *in situ* generation. Unreacted precursor(s) and reaction by-products are also regarded as impurities. Reaction by-products (B) may also be formed during *in situ* generation and are considered as impurities as they are not contributing to the efficacy. Reaction by-products originate from intended reaction(s) of the precursors by complete or incomplete reactions.

Example:

Peracetic acid generated from 1,3-diacetyloxypropan-2-yl acetate and hydrogen peroxide

<table>
<tr><th colspan="6">Precursors</th></tr>
<tr><td>Precursors (P)</td><td colspan="3"> 
1,3-diacetyloxypropan-2-yl acetate</td><td colspan="2"> 
hydrogen peroxide</td></tr>
<tr><td>Composition of the precursors</td><td colspan="3">100%</td><td colspan="2">30% hydrogen peroxide
5% stabiliser
65% water</td></tr>
<tr><th colspan="6">Technical active substance generated in situ</th></tr>
<tr><td>Pure active substance generated in situ</td><td colspan="4"> 
Peracetic acid</td><td>Pure active substance</td></tr>
<tr><td>Reaction by-products (B) (regarded as impurity)</td><td>  </td><td>  </td><td> 
glycerol</td><td></td><td>Impurities of the technical active substance</td></tr>
</table>

Unreacted precursors (regarded as impurities)	 1,3-diacetyloxypropan-2-yl acetate	 hydrogen peroxide	**generated *in situ***
Other impurities (e.g. originating from precursors)	stabiliser		

4. Data requirements for active substances generated *in situ* and their precursors with regard to identity, physical, chemical and physical hazard properties

It is important to note that the precursors are also where relevant managed for other uses through other chemical legislation, such as the REACH Regulation (EU) No 1907/2006 and all related provisions (registration, evaluation, authorisation and restriction) (*CA-Nov15-Doc.5.5-Final_Rev1*[1]). As stated earlier, the data requirements for active substances apply to *in situ* generated technical active substances, while the data requirements for precursors have not been specified.

It is expected that some amount of precursors remain unreacted and then constitute a part of the technical active substance generated *in situ*, where these are considered as impurities. The concentrations of these unreacted precursors might depend on the kinetics of the reaction and might change over time. Therefore, the dossier has also to include sufficient information about the precursors. Hence, the information requirements of Annex II, Title 1 of the BPR apply also to precursors. Consequently, datasets of both the precursors and the technical active substance generated *in situ* shall fulfil the same data requirements.

4.1. Identity

4.1.1. Technical active substance generated *in situ*

The name of the technical active substance is defined by reference to the precursor(s) and the

pure active substance generated and in some cases by the generation process.

The reference specification for the *in situ* generated technical active substance should be set by information about the precursors and the following data should be provided:

- Generation process including the conditions and their variations.
- Information on the precursors and technical active substance generated *in situ:*
    - Maximum applied concentration of the precursors for generation
    - Concentrations of the constituents of the technical active substance generated *in situ* and their variations (normally measured or if not applicable calculated).
- Quality control data of the technical active substance generated *in situ* as an indicator for the level of variation of the composition at different conditions: e.g. pH, temperature, dilution. Further conditions of the generation system and process might be required for product authorisation.

4.1.2. Precursor

The precursors need to be described by their complete composition. Depending on whether the precursor(s) can be regarded as so-called “commodity chemical(s)” the information requirements vary. Quality control data (QC data) or certificates of analysis (CoA) are sufficient for commodity chemicals. Consequently, no analytical methods or analysis under GLP requirements for identification of the precursors need to be provided.

5-Batch analysis conducted under Good Laboratory Practice (GLP) with fully validated and specific or highly specific methods shall be provided for precursors, which cannot be regarded as commodity chemicals. Whether a precursor can be regarded as a commodity chemical will be decided case-by-case by the Member State competent authorities.

4.1.3. Generation process

The generation process shall be described in details and include all parameters with explanation on the impact of the composition of the technical active substance. This information include:

- Reaction scheme (mandatory) and kinetics
- Maximum possible concentration of the pure active substance
- Catalysts and additives needed for the reaction with explanation about their functionalities
- Physical parameters that impact the outcome of the qualitative and quantitative composition of the technical active substance
- For continuous processes, the release per time unit may be needed
- Device description if devices are required for the generation

4.2. Technical equivalence

The assessment of technical equivalence compares whether the hazard of a new source to the approved source(s) of the precursor(s) is equal or lower with regard to the chemical composition

of the reference source(s). Therefore, the technical equivalence assessment of *in situ* generated substances has also to consider the compositions of the precursors and the reactions occurring in the generation process. That means information about the composition of the technical active substance is required. It should also be noted that different precursors generating the same pure active substance are regarded as different technical active substances. Further and detailed criteria will be elaborated in the specific *BPR Guidance on applications for technical equivalence*[2].

4.3. Physical and chemical properties

The complete information requirements according to Annex II, Title 1, Chemical substances of the BPR have to be provided for all precursors and the pure active substance(s) or the technical active substance, as appropriate. It is possible to refer to accepted literature data, as recognised handbooks. In the cases where certain endpoints are not needed or technically not feasible scientific sound waiving justifications have to be provided.

4.4. Physical hazards

The complete information requirements according to Annex II, Title 1, Chemical substances of the BPR have to be provided for all precursors and the pure active substance(s) or the technical active substance, as appropriate. It is possible to refer to accepted literature data, as recognised handbooks. In the cases where certain endpoints are not needed or technically not feasible scientific sound waiving justifications have to be provided.

4.5. Methods for detection and identification

Fully validated analytical methods for the analysis of the precursors as manufactured are only require for non-commodity chemicals. CoA or QC data are sufficient for commodity chemicals. Nevertheless, sufficient information about the precursor's compositions and the applied analytical methods should be described in detail.

Fully validated analytical methods for the analysis of the pure active substance and its impurities are required.

In addition, fully validated analytical methods have to be provided for monitoring according to the criteria explained in the *BPR guidance Volume I Part A, B and C Information Requirements*[3]

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[2] ECHA Guidance on the Biocidal Products Regulation, Volume V: Guidance on applications for technical equivalence, Version 1.1, March 2017. https://www.echa.europa.eu/documents/10162/23036412/guidance_applications_technical_equivalence_en.pdf/18f72d37-98b6-47c8-98bb-941afeff6968

[3] ECHA Guidance on the Biocidal Products Regulation, Volume I: Identity/physico-chemical properties/analytical methodology – Part A, B and C: Information Requirements, Version 1.1, November 2014. https://www.echa.europa.eu/documents/10162/23036412/bpr_guidance_ir_part_vol_i_part_a_en.pdf/35e5761b-8a4a-454a-bfd7-f04b41aa9f2a

for the pure active substance, the precursors and any relevant impurity present in the technical active substance.

5. Efficacy information requirements for precursors of *in situ* generated active substances

The data requirements for active substances (BPR Annex II, Title 1) apply to *in situ* generated active substances, while the situation is not fully clear for precursors.

According to BPR Article 3(1)a, a substance or mixture generating biocidal active substance is a biocidal product, and therefore the starting point for the information requirements should be as indicated in the BPR Annex III, where applicable. In general, the particularity of *in situ* generated active substances is that the "main" cidal effect is always caused by the *in situ* generated active substance. However, the precursors regarded as biocidal products may or may not have some effect on their own right and contribute to the efficacy. It is also expected that some precursors may remain unreacted and constitute a part of the substance generated *in situ.* Therefore, when considering efficacy of *in situ* generated active substances, the whole technical active substance generated *in situ* should be considered, not the precursors separately and information concerning the reaction scheme and description of the completeness of the reaction should always be provided.

Thus, regarding the efficacy for precursors of *in situ* generated active substances the submission of full efficacy data according to Annex II/III of the BPR is not required.

Nevertheless, in some cases at the request of the eCA additional efficacy information on precursors, e.g. the precursor's concentration at the point of application of the active substance tested should be provided for active substance approval. Additional efficacy data or justification may be requested, if appropriate.

5.1. Test substance

With regard to the substance tested for efficacy, as stated in the previous chapter it is necessary to consider the whole technical active substance generated *in situ*. The dependence of the reaction on conditions like pH, temperature, light, voltage, etc. needs also to be considered.

6. Human health risk assessment and implications on data requirements for precursors

6.1. Risk assessment

This section describes the human health risk assessment to be performed to cover the situation before *in situ* generation (6.1.2 Precursors) and during/after *in situ* generation (6.1.1 Technical active substance generated *in situ*).

6.1.1. Technical active substance generated *in situ*

The principles of risk assessment for substances generated *in situ* are the same as for any biocidal active substances and the risk assessment should be performed according to the *BPR guidance Volume III Parts B and C Assessment & Evaluation*[4]. For an *in situ* generated active substance, the context may be different however, as the toxicity data package may have been generated with the pure active substance instead of the technical active substance generated *in situ*.

Human exposure will possibly take place to all constituents of the technical active substance generated *in situ*. It is therefore considered that the substance relevant for risk assessment is the technical active substance generated *in situ*, which according to the definitions in Section 3 of this document comprise the pure active substance, unreacted precursors, reaction by-products and other impurities. Therefore, in addition to the pure active substance and precursors, it is necessary to consider all the constituents of the technical active substance generated *in situ* in the risk assessment.

It needs to be considered whether there may be stable constituents that would remain in the technical active substance generated *in situ* longer than the active substance, or constituents whose concentration could increase over time e.g. due to repeated applications. Such constituents may become toxicologically relevant even if they are initially present at low concentrations.

With regard to constituents that were not tested together with the pure active substance, the following tiered approach should be followed.

- **Tier 1**. All constituents should be assessed to determine whether they, at the concentration at which they are present, have additional or comparable toxicity when compared to the pure active substance. This can be done using any information available, including non-test methods (such as QSARs, read-across) and weight of evidence. The constituent would have additional toxicity if it has a toxic property (e.g. sensitisation, mutagenicity) that the pure active substance does not have. It would have additional or comparable toxicity if it has the same toxic property as the pure active substance, but comparable or higher potency. If there are no indications of additional hazards or toxicity and the relevant NOAEL/LOAEL (No observed adverse effect level/ Lowest Observed Adverse Effect Level) values would not change due to these constituents, then a risk assessment for these constituents is not necessary. Otherwise a Tier 2 assessment would be performed.
- **Tier 2**. For constituents that were in Tier 1 identified as potentially having additional or comparable toxicity when compared to the pure active substance, risk characterisation for combined exposure should be performed according to *BPR*

[4] ECHA Guidance on the Biocidal Products Regulation, Volume III: Human Health, Part B and C: Assessment & Evaluation, Version 2.1, February 2017. https://www.echa.europa.eu/documents/10162/23036412/biocides_guidance_human_health_ra_iii_part_bc_en.pdf/30d53d7d-9723-7db4-357a-ca68739f5094

guidance Volume III Parts B and C Assessment & Evaluation[4].

If the concentrations of the constituents in the technical active substance generated *in situ* are unknown or variable, reasonable worst-case assumptions should be used.

6.1.2. Precursors

Risk assessment is necessary for exposure to precursors taking place before *in situ* generation. The risk assessment will be performed according to the *BPR guidance Volume III Parts B and C Assessment & Evaluation*[4].

The need to perform risk characterisation for combined exposure should be considered, as described above for the technical active substance generated *in situ*.

Following *in situ* generation, the precursors may be present as impurities and will be assessed as indicated above for the technical active substance generated *in situ*.

6.1.3. Considerations on other relevant substances

Reaction by-products are generated together with the pure active substance and may be covered by the toxicity studies performed on the technical active substance generated in situ if the test substance was representative. Where the composition varies e.g. with time, pH or temperature, all relevant information has to be provided by the applicant. Reaction by-products are relevant for the risk assessment of the technical active substance generated *in situ*.

Disinfection by-products may be generated if the technical active substance generated *in situ* (i.e. any of the substances AS, B, P, I) reacts with micro-organisms or other organic matter when exerting its biocidal effect. These by-products need to be taken into account in the risk assessment but are not discussed in this document as they fall under the *BPR guidance Volume V Guidance on Disinfectant By-Products*[5].

Free radicals are discussed in the CA meeting document *CA-May16-Doc 5 1 – Guidance on data requirements for free radicals generated in situ from ambient air and water*[6], which provides advice on the risk assessment of free radicals generated *in situ*, applicable also to free radicals generated from “chemical” precursors. Where systems generating free radicals *in situ* make use

[5] ECHA Guidance on the Biocidal Products Regulation, Volume V: Guidance on Disinfection By-Products, Version: 1.0, January 2017. https://www.echa.europa.eu/documents/10162/23036412/bpr_guidance_vol_v_dbp_new_en.pdf/c7d11d09-8ae5-317f-0eeb-ec8b2aa938b3

[6] CA-May16-Doc.5.1 – Final. Guidance to specify information requirements for free radicals generated in situ from ambient water or air for substance approval in the context of the BPR. https://circabc.europa.eu/d/a/workspace/SpacesStore/7636718f-74fc-4282-8f8f-b0ad4357a0ca/CA-May16-Doc%205%201%20-%20Guidance%20on%20data%20requirements%20for%20free%20radicals%20generated%20in%20situ%20from%20ambiant%20air%20or%20water.doc

of chemical precursors, the principles presented here regarding information requirements, testing and risk assessment are applicable to the assessment of such precursors.

6.2. Implications on data requirements for precursors of *in situ* generated active substances

A risk assessment is necessary for the precursors to demonstrate that the relevant criteria in BPR Article 19 are met. The data requirements for products (BPR Annex III, Title I) would not be sufficient to satisfy the conditions in Article 19 since the risk assessment of a biocidal product is largely based on the data available for the active substance(s) present in the product. Hence, information on all toxicological properties indicated as core data in BPR Annex II, Title 1 is considered necessary in order to perform a risk assessment for the precursors.

It is however considered that the data requirements should not be as strict as they are for active substances, and consequently full studies for many endpoints might not be required based on read-across, QSAR information, weight of evidence, exposure based waiving and publicly available information. In general, flexibility should be applied regarding the fulfilment of data requirements.

To ensure that all information is taken into account in considering the need for further data requirements, the applicants should provide all information available to them on the precursors. Such information might be available e.g. in another legal framework such as REACH.

Performing new vertebrate studies should be avoided where possible.

No data is required if the active substance is generated from precursor substances or mixtures that cannot themselves be authorised as biocidal products (ambient air, seawater).

Information has to be provided on the kinetics of active substance formation and subsequent degradation and/or hydrolysis to enable risk assessment for the relevant substance and composition. The time scale relevant for human exposure should be considered. The typical realistic concentration ranges of precursors and pure active substance in the technical active substance generated *in situ* should be provided. Monitoring data and model calculations can be used as applicable. Sufficient information should be provided on factors affecting the composition of the technical active substance generated *in situ*, such as the equipment used and any relevant parameters, temperature, pH and the presence of organic matter.

The evaluating CA may request additional information when this is deemed necessary for concluding on the risk assessment.

6.3. Waiving

BPR Annex IV

The general rules for the adaptation of the data requirements (BPR Annex IV) are intended to apply for active substances and biocidal products. These rules should mostly be applicable also to precursors, although a higher degree of flexibility is essential in order to avoid unnecessary animal studies.

Biocides Guidance on information requirements

The *BPR guidance Volume III Part A Information Requirements*[7] is also intended to apply for active substances and biocidal products. While these rules should mostly be applicable also to precursors, they cannot be applied in full. The possibilities for waiving according to the guidance are considered too limited. However, where the guidance would allow the waiving of information, this should apply to precursors as well.

REACH Guidance

In the REACH Regulation, the general rules for the adaptation of standard information requirements (REACH Annex XI) are similar to those set in BPR Annex IV. The relevant guidance[8][9][10] is available at the ECHA website and may be used as applicable. It should however be noted that the information requirements are different from the BPR, and furthermore, both the REACH information requirements and the relevant guidance depend on the tonnage level. Overall, careful consideration is necessary in concluding on the applicability of the REACH guidance to a specific information requirement.

Further considerations

Where exposure based waiving for precursors is accepted at the active substance approval stage, it is necessary at the product authorisation stage to assess whether the justification for data adaptation still applies (see also BPR Annex IV, chapter 3.1). Further information may then need to be requested for product authorisation for uses where exposure is expected to be higher and the justification for waiving is not valid.

6.4. Test substance

Precursors

Any testing of precursors should be performed using substances of the same purity as those actually used for *in situ* generation.

Active substance

Regarding the active substance to be tested, the material used in testing has to be considered. Ideally, the technical active substance generated *in situ* should be used, although it must be

[7] ECHA Guidance on the Biocidal Products Regulation, Volume III: Human health, Part A: Information Requirements, Version 1.1, November 2014. https://echa.europa.eu/guidance-documents/guidance-on-biocides-legislation

[8] Guidance on information requirements and chemical safety assessment. Chapter R.5: Adaptation of information requirements. Version: 2.1. December 2011

[9] Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance. Version 4.1. October 2015

[10] ECHA Practical Guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration. Version 2.0 – July 2016

recognised that testing may not always be possible. The active substance generated *in situ* would often not have a stable defined composition, and therefore further consideration should be given to cover, as far as possible, all substances to which exposure may take place, including the pure active substance, precursors, reaction by-products and impurities.

It is necessary to consider the reaction kinetics during *in situ* generation, together with the expected use patterns and label instructions in relation to the relevant time points relevant for human exposure and *in situ* generation. The concentrations of precursors and other constituents varying over time, as well as their dependence on other conditions (pH, temperature, light, presence of organic material etc.) need to be considered.

Special attention has to be paid to the concentrations of the toxicologically most relevant constituents of the technical active substance generated *in situ*, applying reasonable worst-case assumptions.

In practice, testing of the technical active substance generated *in situ* may be difficult or even impossible, and therefore testing of the pure active substance as such should be acceptable, although, as a consequence, the technical active substance generated *in situ* may contain impurities for which further testing might be triggered if appropriate information is not available.

7. Environmental risk assessment and implications on data requirements for precursors

7.1. Approach towards the assessment of technical active substances generated *in situ* with focus on precursors

In general, there are two major assessment approaches possible for the components of the technical active substance generated *in situ*:

Option 1 - Single component assessment: In this approach ecotox and e-fate information is gathered and assessed on single substance component level, i.e. there is a dataset for each component of the substance generated *in situ* (dataset for the pure active substance AS, dataset for precursors P1, P2, etc., datasets for each of the reaction by-products B1, B2, etc. and other impurities I1, I2, etc… in **Figure 1**).

Option 1 should be followed by mixture toxicity screening of the components of the technical active substance generated *in situ* and where relevant eventual mixture toxicity assessment in accordance with the *BPR Transitional Guidance on mixture toxicity assessment for biocidal products for the environment*[11].

[11] ECHA Transitional Guidance on the Biocidal Products Regulation: Transitional Guidance on mixture toxicity assessment for biocidal products for the environment. May 2014. https://www.echa.europa.eu/documents/10162/15623299/biocides_transitional_guidance_mixture_toxicity_en.pdf/4a56f687-d29e-47b4-80c3-38f37e77156a

Option 2 - *In situ* generated technical active substance assessment: In this approach ecotox and e-fate information is gathered on and assessed for whole mixture of the components of the technical active substance as generated *in situ*, i.e. there is a single dataset for whole mixture (technical active substance) comprising the pure active substance, unreacted precursors, reaction by-products and other impurities. I. e. this option assumes there is no ecotox data for single components of the technical active substance generated *in situ*.

Option 2 is applicable where a single component assessment is not possible, the technical active substance is complex or as a refinement of the single component assessment (Option 1). However, while predicted environmental concentration (PEC) values for mixture exposure are difficult to derive, Option 2 is relevant only for specific emission pathways (where there are direct releases to an environmental compartment). For further information on relevant considerations and limitations see the discussion of Tier 4 in the *BPR Transitional Guidance on mixture toxicity assessment for biocidal products for the environment*.

Note that the in the **following chapters 7.1.1 to 7.1.3 the focus is on Option 1.** Option 1 is preferred option as it deals with information which is easier to generate and use and is more adaptable. Some clarifications however on Option 2 are also given. Nevertheless, it must be judged case-by-case which option is applicable for the case at hand.

7.1.1. Risk assessment

The information submitted should be sufficient to demonstrate that the relevant criteria in BPR Article 19 are met.

The following general principles should apply for the environmental risk assessment of precursors:

- Mixing and loading of precursors is generally not relevant for environmental exposure. Therefore the possibility of release of precursors to the environment would normally be assessed only after *in situ* generation.
- The exposure assessment of precursors should consider all scenarios that are relevant for the pure active substance generated *in situ*.
- Risk assessment of precursors should consider the concentrations of unreacted precursors. Reliable information on the amount/concentration of an unreacted precursor in the technical active substance generated *in situ* should be provided, including the kinetics and its variability if relevant. The concentrations of unreacted precursors varying over time, as well as their dependence on other conditions (pH, temperature, light, presence of organic material etc.) need to be considered. If the amount/concentration of unreacted precursor in the technical active substance generated *in situ* is unknown or variable, worst case assumptions should be used. In extreme cases up to 100% precursor could be assumed to remain unreacted (it is expected that where the composition of the technical active substance generated *in situ* varies e.g. with time, pH, temperature, all relevant information will be provided by the applicant and it will cover also other components in addition to the unreacted precursors).

- Risk assessment should include screening to assess the relevance of mixture toxicity assessment for the technical active substance generated *in situ* and where relevant should be followed by the mixture toxicity assessment.

A more specific risk assessment strategy is provided in **Figure 3** in the next chapter 7.1.2. **Figure 3** illustrates the risk assessment strategy for precursors linked to the information requirements for precursors. As the triggers for information requirements are equally applicable to the risk assessment, clarification of this strategy is provided only once (i.e. in chapter 7.1.2). This strategy is considered applicable to the reaction by-products (B1, B2, in **Figure 1**) of the technical active substance generated *in situ*. Case-by-case judgement may nevertheless be relevant for the reaction by-products of the technical active substance generated *in situ*, in particular when they are transient or not possible to isolate.

ECHA will coordinate development of matrix/core dossiers for precursors or reaction by-products in order not to repeat evaluations for those substances that appear across different active substances generated *in situ* which will be available to the competent authorities. Similar rules of access to the MS and applicants will apply as those applied when evaluating active substances with multiple applicants. This will not *per se* change the obligation of the applicants to comply with the information requirements on precursors/reaction by-products as given by this document.

7.1.2. Implications on data requirements for precursors of *in situ* generated active substances

For the pure active substances generated *in situ* (substance “AS” in **Figure 1**), the information requirements for active substances specified in Annex II, Title 1 of the BPR apply.

According to BPR Article 3(1)a, a substance or mixture generating biocidal active substance is a biocidal product, and therefore the starting point for the information requirements should be as indicated in BPR Annex III, Title 1 where applicable. However, environmental data requirements specified in Annex III are designed for “mixtures” and are usually referring back to their individual components. Annex III requirements are therefore not appropriate for situations where precursors are single substances. Based on these considerations, it is proposed to adapt the environmental data requirements given in BPR Annex II, Title 1 to the precursors of *in situ* generated active substances.

The *draft Guidance on Substances of Concern*[12] clarifies that the BPR requires that a risk assessment is performed for all active substances and substances of concern (SoC) in a biocidal product individually as well as an assessment of potential cumulative/synergistic effects, i.e. also a mixture toxicity assessment is required. Considering the definition of a precursor as a biocidal product, the principles of the *draft Guidance on Substances of Concern*[12] should be relevant for

[12] ECHA Guidance on the Biocidal Products Regulation, Volume IV: Environment - Assessment and Evaluation (Parts B + C), Public DRAFT Version 2.0. June 2017. https://www.echa.europa.eu/documents/10162/23047722/bpr_guidance_vol-iv_env_part_bc_draft_ca_en.pdf/13459e06-ecf7-85d8-d4d4-eaa5806b6dbf

the assessment of precursors in the context of active substance approval.

To address the complexity of the evaluation of active substances generated *in situ*, the following elements should be considered to identify precursors relevant for risk assessment:

In principle no data and no risk assessment needs to be provided for precursors that are substances or mixtures, which cannot themselves be authorised as biocidal products, such as air, seawater. If such precursors are other than air or seawater, it is necessary to consider in cooperation with the eCA whether information is needed. Appropriate justification for non-submission of data needs to be provided by the applicant.

For any other precursors it is proposed that Annex II, Title 1 requirements on each of the precursors are applicable if:

- the precursor is not consumed fully in the *in situ* generation of the active substance (or there is insufficient information to support that it is fully consumed) and
- its release to the environment cannot be excluded and
- it is a substance of concern (see *draft Guidance on Substances of Concern*[12]) or its status is unknown or
- the precursor is present in the technical active substance generated *in situ* at >5%.

The strategy for the identification of precursors relevant for risk assessment is illustrated in **Figure 2**.

For the precursors fulfilling the above-mentioned criteria, Annex II, Title 1 data requirements for precursors are limited to those triggered by risk assessment as provided in the following stepwise approach (**Figure 3**):

> **Step 1:** Using aquatic acute toxicity data (sections 9.1.1, 9.1.2, 9.1.3, 9.1.5 of Annex II, Title 1) to derive predicted no effect concentration (PNEC) values, assuming no degradation, using substance solubility, vapour pressure and log P_{ow} (the latter as basis for a QSAR estimate of partition coefficients) to estimate the fate and distribution in the environment. If under these assumptions, PEC/PNEC ratio is <1, i.e. the risk is acceptable, no further data is required. Otherwise, proceed to step 2.
>
> **Step 2:** Conduct relevant environmental fate and behaviour studies (section 10 of the Annex II, Title I). Refine the exposure assessment using the degradation rates or measured partition coefficients from these studies. If PEC/PNEC ratio is <1, i.e. the risk is acceptable, no further data is required. Otherwise, proceed to step 3.
>
> **Step 3:** Provide long-term toxicity data (sections 9.1.6, 9.3 of Annex II, Title 1). Refine the assessment factors/PNECs and the risk assessment. If PEC/PNEC ratio is <1, the risk is acceptable. Otherwise, conclude there is a risk/evaluate RMMs.

The comparison of PEC and PNEC values in the stepwise approach above is assumed to be on single component level. When PEC/PNEC ratio is <1 and there is another component of the technical active substance generated *in situ* released to the same compartment, mixture toxicity assessment has to be further performed and additional information requirements may be triggered on the basis of the tiered approach stipulated by the *BPR Transitional Guidance on mixture toxicity assessment for biocidal products for the environment*[11].

Figure 2 Identification of precursors subject to risk assessment

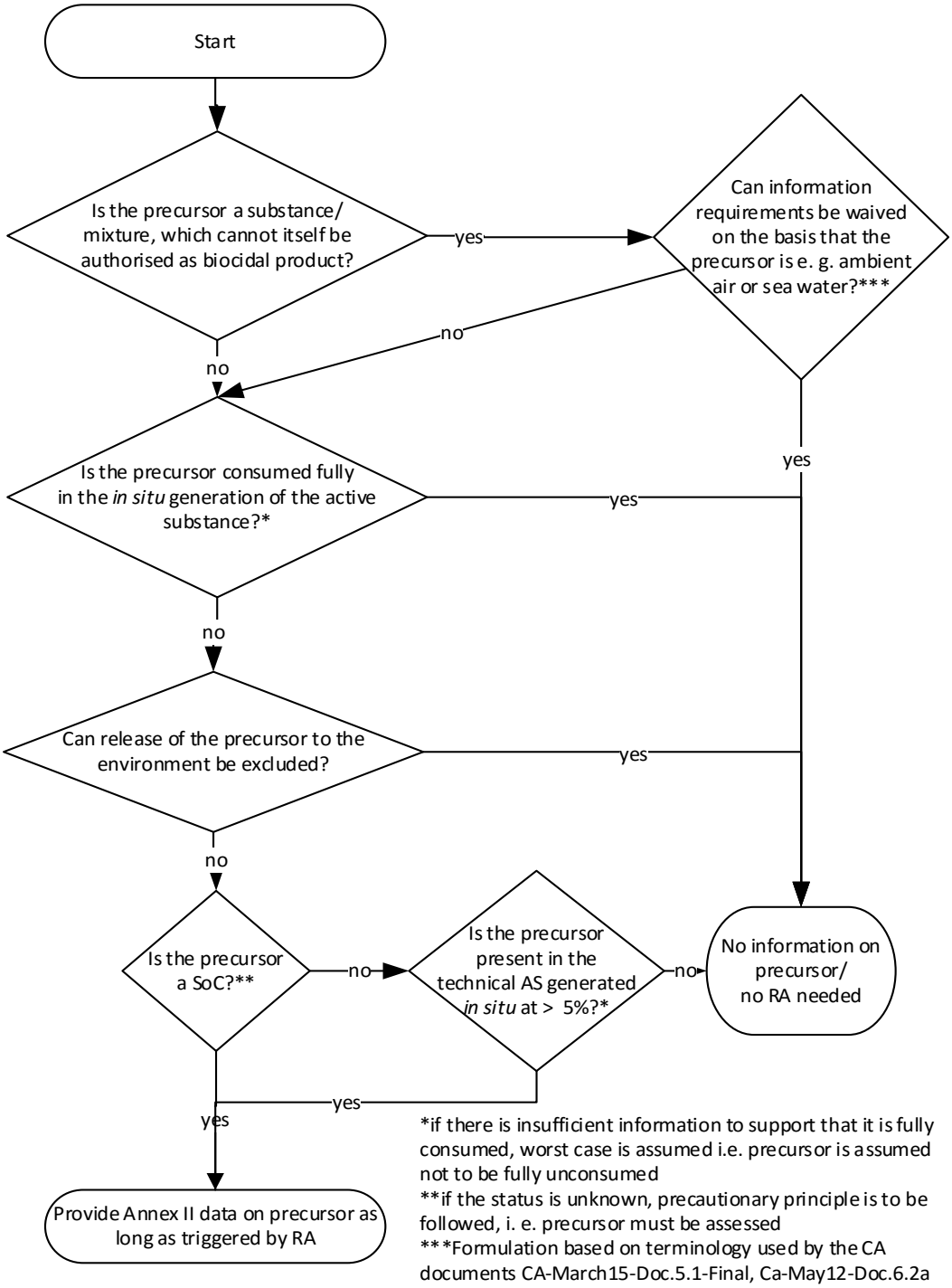
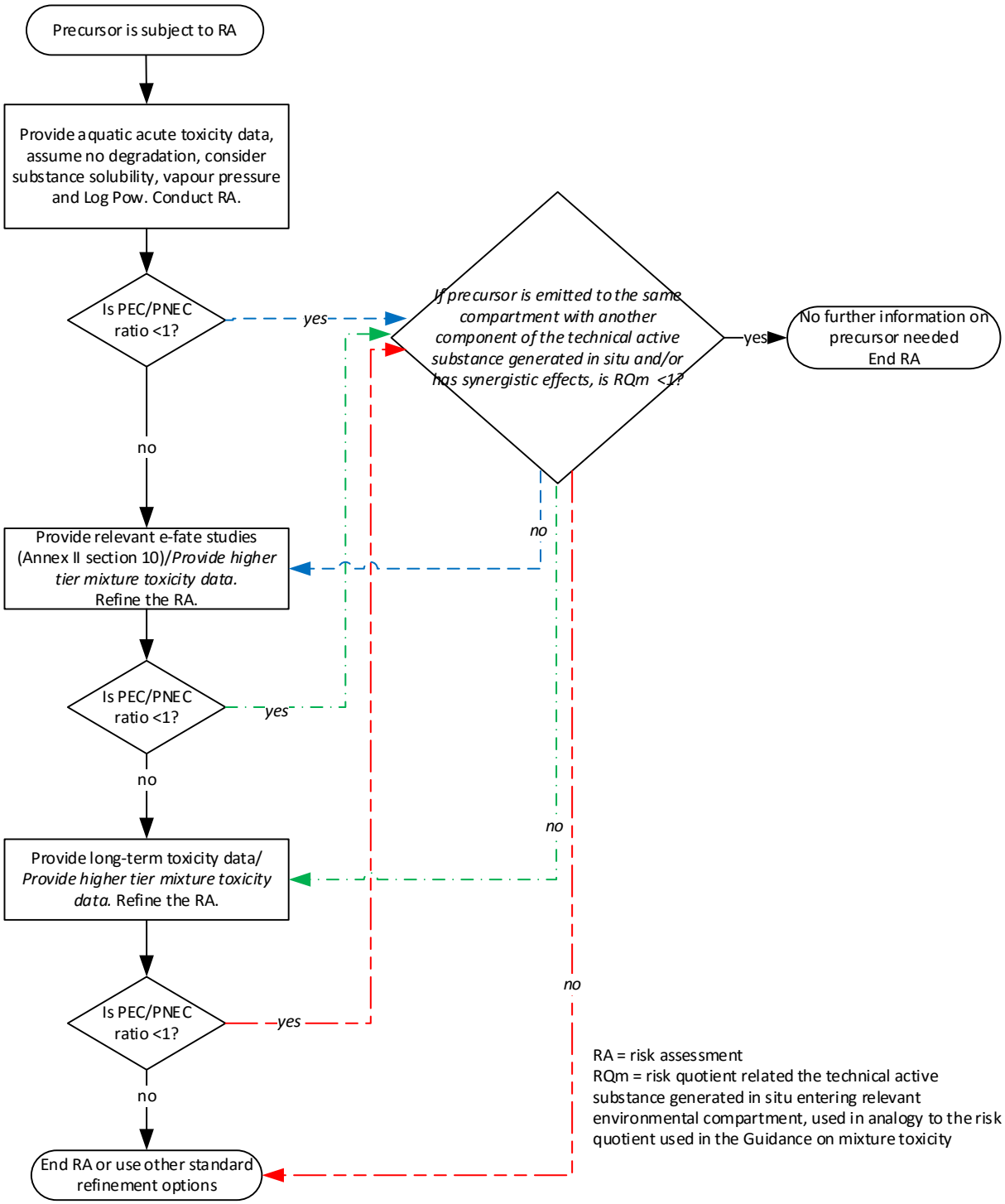


Figure 3 Information requirements for precursors relevant for risk assessment



Additional considerations on data necessary to support the risk assessment:

Further information needs may be triggered by product-type specific additional data set (ADS) requirements which are equally applicable to precursors as for active substances (see chapter V of the *BPR guidance Volume IV Environment Part A Information Requirements*[13]).

The approach described above is relevant in particular to data poor substances. Where there is abundance of data, the user should proceed to the next appropriate step of the assessment strategy.

The possibility to use information retrieved from material safety data sheets, EU or international chemical reviews, QSARs, read-across, data waiving and use of literature data for precursors should be considered case by case, considering in particular that due to the transient nature of certain *in-situ* generated substances, many tests might not be possible. Grouping of substances is particularly relevant when addressing substances generated *in situ* with high number of components (as proposed in the *BPR guidance Volume V Guidance on Disinfection By-Products*[5]). Draft *Guidance on Substances of Concern*[12] provides further useful guidance on gathering data and performing risk assessment relevant to assessment of precursors.

In accordance with the competent authority meeting document (*CA-Nov15-Doc.5.5 Final_Rev 1*[1]), PBT assessment and endocrine activity identification of precursors are not required.

QSAR may be used to assess whether the precursor fulfils the SoC criteria.

Where the applicant wishes to refer the authorities to the relevant data on precursors submitted under another legal framework such as REACH, the applicants are required to provide the authorities with the access to these data. Where the information requirements under BPR for precursors are not fully addressed by the data available under REACH, at least the missing information must be provided in the submission under the BPR. In any case, the risk assessment for such precursors where they fulfil the criteria outlined in **Figure 2** shall always be provided in the BPR submission.

Additional considerations for Option 2 - *In situ* generated technical active substance assessment:

The risk assessment is limited to the compartments with direct release. PEC and PNEC are then derived for the whole mixture comprising of components of the technical active substance generated *in situ* in similar manner as for single substances and a corresponding risk characterisation can be performed for the whole mixture (technical active substance) generated *in situ*.

[13] ECHA Guidance on the Biocidal Products Regulation, Volume IV: Environment - Part A: Information Requirements, Version 1.1, November 2014. https://www.echa.europa.eu/documents/10162/23036412/bpr_guidance_ir_part_vol_iv_part_a_en.pdf/e5ffe222-c4ae-40c7-8306-83645e52aca2

7.1.3. Test substance

The tests with precursors should be performed using material of the same purity used for *in situ* generation.

In general, ecotox and e-fate data should be established for the pure active substance generated *in situ* and relevant precursors in isolation (for the precursors following the strategy outlined in chapter 7.1.2 above) and not for the technical active substance as a whole. This is to be able to address the distribution in the environment that can be substance specific. This consequently allows then comparison of appropriate PNECs with appropriate PECs during risk characterisation.

Additional considerations for Option 2 - *In situ* generated technical active substance assessment:

The chemical composition of the initial technical active substance generated *in situ* may change during the exposure, as the different chemicals might have a different stability and distribution between the different compartments in the test. Such processes can be accounted for by testing the ultimate, environmentally relevant technical active substance generated *in situ* instead of the original technical active substance generated *in situ*.

7.2. Considerations on other relevant substances

Reaction by-products are proposed to be treated in the same manner as precursors.

If the technical active substance generated *in situ* (i.e. any of the substances AS, P, B or I) reacts with organic matter when exerting its biocidal effect, disinfection by-products (DBP) may be generated. These by-products fall under the *BPR guidance Volume V Guidance on Disinfection By-Products*[5].

The CA meeting document *CA-May16-Doc 5 1 – Guidance on data requirements for free radicals generated in situ from ambient air and water*[6] provides advice on specifics of risk assessment of free radicals generated *in situ*. Where systems generating free radicals *in situ* make use of “chemical” precursors, the principles regarding information requirements, testing and risk assessment outlined in the current document are applicable to the assessment of such precursors.

If the unconsumed precursors degrade in the environment, their degradation products (metabolites) must be tested/assessed in standard ways as would be done for degradation products for non *in situ* generated active substances. The same principles of metabolites assessment apply as those outlined in the *BPR guidance Volume IV Environment Part A*

Information Requirements[14] *and Part B Risk Assessment*[15].

[14] ECHA Guidance on the Biocidal Products Regulation, Volume IV: Environment, Part A: Information Requirements. Version 1.1. November 2014. https://www.echa.europa.eu/documents/10162/23036412/bpr_guidance_ir_part_vol_iv_part_a_en.pdf/e5ffe222-c4ae-40c7-8306-83645e52aca2

[15] ECHA Guidance on the Biocidal Products Regulation, Volume IV: Environment, Part B Risk Assessment (active substances). Version 1.0. April 2015. https://www.echa.europa.eu/documents/10162/23036412/bpr_guidance_ra_vol_iv_part_b_en.pdf/e2622aea-0b93-493f-85a3-f9cb42be16ae