Best Practices for in-situ applications [and remaining issues]

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Good Bacteria
- Lactococcus
- Lactobacillus
- Lactobacillus bifidus

Bad Bacteria
- Clostridium perfringens
- Staphylococcus
- Escherichia coli
Subjects to be treated

- In-situ development **before** re-definition 2015
- In-situ development **after** re-definition 2015
- How to deal with products
- System approach [role of devices]
- Art 54 BPR & Cluster formation
- Free radicals
History and background – Regulatory status BPD vs. BPR

Result of a lack of a clear guidance for the regulation of in-situ generated active substances under the BPD:

Either the precursor was notified (e.g. ammonium sulphate for the generation of monochloroamine from sodium hypochlorite; the in-situ generated active substance monochloroamine was not notified; [sodium hypochlorite is an active substance on its own and was notified and supported]
History and background – Regulatory status BPD vs. BPR

Result of a lack of a clear guidance for the regulation of in-situ generated active substances under the BPD:

- or only the in-situ generated active substance was notified (e.g. peracetic acid generated from TAED and sodium percarbonate; the precursors were identified, not notified).

Result: In all of these cases, the notifications performed were honored and the precursor(s) were allowed to remain on the market until a decision was made on Annex I listing (i.e. approval) for the active substance generated in-situ from the concerned precursor(s).
ISG and precursors – definitions, reaction types and examples

1. In-situ generation of the biocidal active substance during use:

**Principle:** The biocidal active substance is generated in-situ as a result of a decomposition or reaction from a single precursor under use conditions such as heating, combustion e.g. The **precursor** may be a biocidal active substance in its own right or may not have itself any significant biocidal effect on the target organisms.

**Examples:**
- Aluminium/Magnesium phosphide releasing $\rightarrow$ phosphane
- Various Substances releasing $\rightarrow$ formaldehyde
2. Hydrolysis to form an acid-base pair

The biocidal active substance is formed in-situ only as an immediate consequence of the addition or dilution of the precursor to water = *hydrolysis* → The precursor and in-situ active substance are related as an acid-base pair.

In such cases, the formation of an in-situ substance active may be an unavoidable consequence of the use of the precursor in water at a given concentration, temperature and pH. This adds a kinetic dimension to the substance definition (peer review by APCP WG necessary)
Examples of Hydrolysis to form an acid-base pair:

- Sodium percarbonate releasing **hydrogen peroxide**
- Chlorine / **hypochlorous acid** / hypochlorite
- Substituted hydantoin hydrolysing to **hypohalous species**
3) Chemical reaction:

Principle: Two or more substances (precursors) are reacting with each other prior to or during the application to generate other biocidal active substances in-situ.

The initial substances may or may not possess biocidal activity and are placed on the market with the intention of generating the active substance(s) in-situ.
Examples of chemical reaction*

Ammonium salts and sodium hypochlorite $\rightarrow$ chloramines
Tetraacetylethlenediamine (TAED) and per oxygens $\rightarrow$ peracetic acid

Halide salts and oxidants generating $\rightarrow$ hypohalous species

Sodium chlorite reaction with a strong acid $\rightarrow$ chlorine dioxide
Sodium chlorate, with hydrogen peroxide and presence of a strong acid, $\rightarrow$ chlorine dioxide
Sodium chlorite reacting with Potassiumperoxomonosulphate $\rightarrow$ chlorine dioxide

*(with or without device)
4) Electrolysis and electrical generation:

The biocidal active substance is generated in-situ from one or more substances by the action of electricity (= electrolysis).

If the generating equipment is supplied with a biocidal claim or used as such and the substance(s) for generating the biocidal is supplied explicitly for use in the equipment generator the biocidal active substance are considered as a biocidal product.

How about Art 54 of BPR in the case of equipment?
Examples of electrolysis and electrical generation:

Sodium chloride generating **hypochlorous acid** via electrolysis
Sodium chlorite generating **chlorine dioxide** via electrolysis
**Ozone** via electrical discharge in air
**Ozone** via electrical discharge in oxygen
**Ozone** via electrolysis of water
Core message(s) of CA proposals of “CA-July13-Doc.5.1.1” and “CA-March15-Doc.5.1-Final, Revised on 23 June 2015” (2):

- All in-situ generated active substances should be notified/defined with the respective precursor(s) they are generated from → all possible in-situ active substance/precursor combinations would have to be notified. → CA-March15 documents!

- In case of other precursor systems/combinations: An application would also have to be submitted for precursors not covered by the in-situ dossier currently under examination for the respective active substance.
Core message(s) of CA proposals of “CA-July13-Doc.5.1.1” and “CA-March15-Doc.5.1-Final, Revised on 23 June 2015” (2):

- CA proposal also included timelines for submission of a declaration of intention and make a notification to ECHA to take over the role as participant as well as for the submission of an application to require the approval of the respective in-situ systems (i.e. the preparation of complete AS dossiers)

- Notifications were only possible (but required) for precursor combinations not already covered by the re-defined identity!
## Re-definition ISG 2013-2015

### Annex I

#### In situ generated active substances

<table>
<thead>
<tr>
<th>Current name</th>
<th>Current precursor(s)/active substance combinations</th>
<th>Additional precursor(s)/active substance combinations</th>
<th>RMS</th>
<th>Legal basis for taking over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium sulphate</td>
<td>Monochloramine generated from ammonium sulphate and a chlorine source</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Monochloramine generated from a mixture of ammonium sulphate and diammonium hydrogenorthophosphate and a chlorine source</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Monochloramine generated from ammonia and a chlorine source</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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In the BPR, the **data requirements on the active substance(s) and the biocidal product are provided for in Annexes II (a.s.) and III (b.p.).**

Due to the lack of a clear-cut guidance, data requirements and the quality of data needed for in situ systems is not well defined/adopted yet.

Discussions in the **CA** on data requirements for in situ generated active(s) and precursor(s) are **ongoing.**

The **APCP WG** compiled recommendations for in-situ in April 2017

The July 2018 **Guidance on TE** postponed in-situ
Product approval ISG after re-definition

Example of an in-situ generated active substances and the precursor system it is generated from:

- Peracetic acid (PAA) generated in-situ from the precursors TAED and sodium percarbonate:

  \[ 2 (2 \text{Na}_2\text{CO}_3 \cdot 3 \text{H}_2\text{O}_2) + 3 \text{TAED} \rightarrow 4 \text{Na}_2\text{CO}_3 + 3 \text{DAED} + 6 \text{PAA} \]

- Precursor suppliers on Art 95 are not necessarily reference suppliers according to Art 54!! Hence \(\rightarrow\) TE (costly !)

- Products formulators have to submit Technical Equivalence data in their product dossier if their supplier is not doing that himself

- In this in-situ system there is fortunately no device needed

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Devices play a key role in particular for **oxidative** biocides.

The variable parameters in devices are very different and a function of the particular active substance which they are bound to produce.

These parameters need to be well understood and described in the **PhysChem** part of the active substance dossier.

If formation of **DBP’s** is to be expected (frequently a function of pH and TOC of the water being used in **electrolytic** processes) testing series under worst case assumptions become necessary.
Depending on the kinetic behaviour of the system these worst case testing series may have to be repeated at several times during the generation reaction.

**Question:** Is the electrode material part of a reference in-situ product? (relevant for electrolytically generated substances)

**Question:** How to prevent the user from modifying important parameters? (relevant for electrolytically generated substances and ISG via chemical reactions)

**Clustering of devices must not make Article 54 of BPR superfluous**
ISG: Role of Devices under BPR

Devices itself should become subject to standardization by appropriate TCs of CEN

In the alternative the fast technical progress in digitalization will cause European devices users to import this equipment from other parts of the world (resulting in no chance of control by national BPR enforcement)
Free Radicals (FR) and Art 93

Discussions at Competent Authority Meetings

- 2003 - 2005  Barley Straw (photocatalyst)
- 2005 - 2009  Ballast Water (TiO₂)
- 2015 - ???  General Principles

2015 discussion centered around
- FR and Disinfection By-Produts
- What is different between FR and just re-defined in-situ actives?

- The method by which FR are generated becomes decisive (case by case decision)
Free Radicals (FR) and Art 93

From 45 ISG substances dossier 23 were FR

RMS are

- 17 Netherlands
- 4 Austria
- 2 UK (before Brexit !)

From 26 PT/a.s. combinations 9 were FR
Thank you for your attention!

It has been a pleasure to participate in the Biocides Day 2018.