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The need for a holistic approach on in-can preservatives

The risk of losing effective in-can preservation
Impact on water based products of several downstream user sectors

October 2014

Introduction

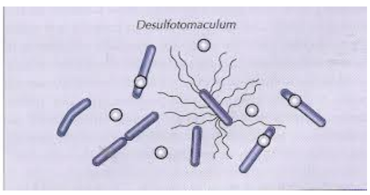
CEPE, together with FEICA, A.I.S.E. and EPDLA, raised their concerns on the recent developments concerning in-can preservatives under the biocide review of active substances during the May 2014 Biocide Competent Authority Meeting (see document CA-May14-Doc.4.4 - Approvals of PT6). This topic was deemed to be of interest and timely, and industry was offered the opportunity to further comment on the potential impact that recent or upcoming decisions may cause. This should allow for a better understanding of the importance of in-can preservatives in order to ensure that informed decisions are made based on a holistic approach of the problem.

This paper first describes the micro-organisms to control in water based products, the available active substances supported for PT6, their activity on the different micro-organisms to control, as well as their advantages and their limitations. It then looks at different 'BPR[1] approval scenarios' and their potential impact in a number of downstream sectors: water born paint, resins, adhesives and detergents.

Micro-organisms to control in water based products

Bacteria, fungi and yeasts.

There are multiple species of bacteria: *Pseudomonas aeruginosa*, *bacillus subtilis, Esterichia coli, Acetobacter aceti, Staphylocossus aureus, Desulphotomaculum, Micrococus* etc. *Pseudomonas* sp is present already in tap water and in 90% of the contamination cases.

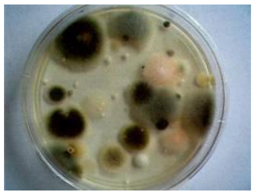


There are multiple species of fungi: *Alternaria alternata, Aspergilius niger, Cladosporium sp, Penicilium sp., Geotrichum* etc.

[1] Biocide Product Regulation 528/2012

There are different sorts of yeasts as well, such as *Sacchamomyces cerevisae, Candida albicans, Rhodotorula* etc.

Damages caused



The damage caused by such micro-organisms on products or on equipment are varied: change of viscosity, change of pH, generation of bad smell, change of colour, destruction of the product ingredients with associated loss of product function/efficiency, generation of gas, visible surface growth and biofilm formation, human health risk (infection, allergies, etc.)[2].

This is why the biocidal control of micro-organisms, which have the capacity to grow fast in the presence of water and organic matter at ambient temperature, is essential. Microbiologically deteriorated products usually have to be destroyed if they cannot be sanitized with biocides.

The problems to solve are twofold

a) preservation of water based products: the treated articles paints, inks, detergents, emulsions.
b) ensuring good plant hygiene to allow continuous manufacturing activities and reduction of the contamination of products.

Due to the environmental legislation on the use of solvents, the paint and adhesive sectors successfully moved to water based products and thereby significantly reduced the emissions of volatile organic compounds in the atmosphere. In the area of liquid detergents there is no other option than water based products (except niche products). Water based products require protection against the development of micro-organisms in the can. Without protection, the product would deteriorate and become waste within a few days.

Even before being placed in the can, during the manufacture (mixing processes) of e.g. paint, inks or adhesives, water based raw materials like polymer dispersions require in-can preservation in order to ensure the quality of the product and avoid microbial deterioration. Good plant hygiene is common practice in order to control the sources of contamination and therefore to minimise the use of in-can preservatives. The use of biocides in plant hygiene is essential and cannot be entirely stopped. If not controlled appropriately, microbes will form biofilms in e.g. pipes. Such biofilms are very hard to control. Microbes inside biofilms are more likely to develop tolerance. The blocking of pipes due to the formation of biofilms ("fouling") can ultimately lead to stopping production. The more infection is present in the plant equipment, the more biocide will be needed in the can.

[2] At a recent dermatologist congress (European Society of Contact Dermatitis, annual congress June 2014, Barcelona), some lead dermatologists warned about the risk to Human Health of using preservative-free cosmetics. They also expressed concerns with the removal of key active substances (Dr. Donald Besito, "Cosmetic preservation: managing risk while maintaining benefit")

Properties required for biocide active substances

- ✓ Broad spectrum of action
- ✓ Fast speed of control
- ✓ Long-lasting action
- ✓ Safe for use for Human Health and the Environment
- ✓ No side effects in the formulation (pH, colour, odour, viscosity, cross linking etc.)
- ✓ High water solubility
- ✓ Easy to formulate
- ✓ Cost effective at recommended use level

For these reasons the substitution of an active is difficult

Currently available in-can preservative active substances on the EU market of relevance to our sectors

In this paragraph we present a brief overview of the in-can preservatives, based on our knowledge as formulators.

The most widely used in-can biocide substances come from the isothiazolinone- and from the formaldehyde releaser- families. They are most efficient and most compatible with the end-products.

Formaldehyde releasers act with different kinetics. Some will release formaldehyde immediately in contact with water, others will release it much more slowly depending on the environment where they are placed. The release of formaldehyde is a matter of chemical equilibrium where its removal will drive the reaction towards further release. These substances are good bactericides but present some weaknesses on other microorganisms. In paint they allow headspace protection (the air in the can).

Among the isothiazolinone family, CMIT/MIT (3:1) was a reference until it was classified about 10 years ago with a low limit for skin sensitization (15 ppm). Its use dropped because our industries do not sell consumer products classified as skin sensitizers, and the market largely switched to a combination of MIT and BIT. MIT is known to control well *Pseudomonas* sp., a family of bacteria that is almost always present in cases of contamination. Some tolerances have been observed with bacteria, and therefore their use in combination with other actives is needed in some specific applications and conditions.

These two families are often used in combination.

Many of the other existing active substances show limitations in use. Some of them currently available on the market are solely used to clean up manufacturing plant equipment, others to clean up contaminated raw materials before the formulation stage. Some only offer fungicidal activity. Many present technical limitations, which differ between sectors.

The isothiazolinones are the main preservative family used in detergents and cleaning products. In addition to their outstanding efficacy in a broad spectrum of activity the two key advantages are their stability at a wide range of pHs and their compatibility with enzymes, a technology used in laundry liquid detergents (most preservatives destroy enzymes). This family is also almost always used in the other industries.

Furthermore, besides the technical needs, in-can preservatives are selected on the basis of their safety profile. There is a large uncertainty on the future classification of active substances which rarely come through their review by RAC with fewer hazard statements.

An overview of the 47 existing biocide actives under the review program, with some comments on their technical limitations in specific applications, is provided in Annex I. It illustrates why the choice of alternatives is often very limited for formulators for various technical reasons, such as chemical incompatibility, discoloration, limited efficacy, smell etc. The two main families of in-can preservatives used by our industries comprise 18 of these substances: 13 formaldehyde adducts[3] and 5 isothiazolinones.

Three applications for new active substances have been made for PT6, namely MBIT, folpet and silver nitrate. The first is another isothiazolinone, the second is an old fungicide used in agriculture and for which PT6 is likely not a main target as it quickly hydrolyzes at typical pH of common products, and the last one has limitations in efficacy. In the short/ medium term, we do not expect much innovation in this area, hence we have to rely on existing ones.

Current threats under the BPR review of active substances

Threat No 1: If formaldehyde releasers become classified as Carc 1B on the basis of the pure formaldehyde classification leading to the non-approval of these actives under the exclusion criteria. Final decisions have not been made yet but ongoing debates suggest that this threat cannot be excluded.
On the one hand the explanation proposed by a Member State is that the releaser breaks down in contact with biological tissues and hydrolyses to formaldehyde, consequently the toxicity of the parent compound is related to the toxicity of formaldehyde. Although the formaldehyde releasers have different kinetics of release/degradation, as soon as this logic would apply it would apply to all of them.
On the other hand the CLP Regulation (Article 5.1) states that the classification should be based on "*the forms or physical states in which the substance is placed on the market and which it can reasonably be expected to be used*". If that argument stands then only the biocide substances that are classified as Carc 1B (i.e. containing at least 0.1% of free formaldehyde) should fall under the exclusion criteria.

> *Article 5*
>
> **Exclusion criteria**
>
> 1. Subject to paragraph 2, the following active substances shall not be approved:
>
> (a) active substances which have been classified in accordance with Regulation (EC) No 1272/2008 as, or which meet the criteria to be classified as, carcinogen category 1A or 1B;

[3] The terms 'adduct' or 'releaser' are used in the document for the same substances.

Threat No 2: the isothiazolinones are all skin sensitisers, although of different potencies. The CMIT/MIT 3:1 mixture was classified 10 years ago with a low specific concentration limit for skin sensitisation at 15 ppm. Since then its use has dropped significantly, typically having been replaced by a mixture of BIT and MIT. In the recent 2-3 years dermatologists have expressed concern on the use of MIT in certain products because of a sudden increase of allergic contact dermatitis in the general population, associated with exposure to MIT in specific uses, and in December 2013 the SCCS made an opinion on the potency of MIT[4].

It is of utmost importance for our sectors that this family of actives remains available for all water based products as today there is no practical substitute for them.

Threat No3: the development of tolerance by micro-organisms, which is an existing problem on its own and potentially an increasing one as a consequence of the two first threats. It is well know that in order to prevent the development of tolerance, a wide range of mode of action is needed.

Bacteria can double their population within 20 minutes in appropriate environments, and this fast reproduction activity also means that their adaptability to new environments can be quick. It is therefore key to maintain different chemical tools acting in different ways.

Evaluation of different potential scenarios

Scenario 1. No effective in-can preservative remains

Without in-can preservatives the industry would have either to stop producing water based products or the entire supply chain until the end-consumer would have to keep products in sufficiently cold conditions to limit the development of micro-organisms.

The first option would be against the European legislation on emission of volatile organic carbons (1999/13, and 2004/42 for paints) and would counter the eco-label scheme and the sustainable development activities. It would also increase the concentration of VOCs in indoor air. When discussing the implementation of the 2004/42/EC Directive, an independent study done by the Commission concluded that ' *The total benefits of reducing 279 kilotonnes of VOCs in the EU is estimated to bring annually health related benefits of €582 million. It should be noted that some benefits were not monetised. These unmonetised effects are the improved health of painters (due to less solvent exposure) and the benefits to ecosystem (due to lower ozone concentrations)'*[5]

[4] EU Scientific Committee on Consumer Safety. Opinion on methylisothiazolinone (P94). Submission II (sensitization only). 12 December 2013

[5] THE COSTS AND BENEFITS THE REDUCTION OF VOLATILE ORGANIC COMPOUNDS FROM PAINTS. Prepared by Directorate general for the Environment, Air and Noise Unit, 2 May 2002. Downloadable at : http://ec.europa.eu/environment/air/pollutants/stationary/paints/paints_legis.htm

The second option would mean that all players in the supply chain would need to acquire cooling equipments, including end users like professionals and consumer, which is unrealistic and energy intensive.

Cooling can reduce the proliferation of micro-organisms but only for a short duration (our products cannot be frozen, just cooled) and this solution cannot offer a satisfactory shelf life. This has a second consequence: smaller batches and associated lower production efficiencies, higher turnover, increased costs. Besides the economic impact, this solution would be against sustainable development due to the high use of energy and raw materials.

To the best of our knowledge there is no chemical alternative. The option of pasteurization/sterilisation is not possible due to the destruction of the properties of the products and lowering the pH or increasing it to levels that are toxic to micro-organisms is only in rare cases an option and could increase the risk of more accidents during handling and/or application.

Scenario 2. The two main families of actives (formaldehyde releasers and isothiazolinones) are no longer available

Given the low number of effective alternatives the conclusion from this scenario is similar to the conclusions of the first scenario. Today it is not possible to effectively control the wide variety of micro-organisms without two main families of in-can preservatives. The water based decorative paints represent around 75% of the total decorative paints sold in Europe for a turnover >5 billions €. Liquid laundry detergents have replaced powder detergents for a number of reasons including energy consumption. Most of them need to be preserved. Certain types of detergents can simply not be made in solid form (institutional products, window cleaners, polishes etc.).

Scenario 3. The formaldehyde releasers are excluded and either all or only part of the isothiazolinones remain

3a. Only part of the isothiazolinones remain

The only effective bactericides available for in-can preservation in the isothiazolinones family are: BIT, MIT, the 3:1 mixture CMIT/MIT. They all have their advantages and their drawbacks (efficacious amounts, spectrum of action, sensitization potency). Terry M. Williams[6] studied the mode of action of the isothiazolinones and concluded that '*The results of these studies showed that the five different isothiazolinone biocides have strong similarity in their basic antimicrobial mechanism of action. Some variations are observed in rate of inhibition, cell binding, transport, and chemical properties which may collectively influence the activity of certain molecules versus certain groups of bacteria, fungi and alga*'. There is no 'one fit all' solution at acceptable dosages.

The elimination of one of them will lead to an increasing use of the others at higher doses, which is not desirable.

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[6] Terry M. William. The mechanism of action of isothiazolinone biocides. Power Plant Chemistry 2007, 9(1).

3b. All of the isothiazolinones remain

A precedent has been set in France a few years ago with a national measure that effectively considered that any products containing formaldehyde or any process generating it has such potential adverse legal consequence for the plant owners that the use of formaldehyde releasers dropped. At most this indicates that their use can be reduced, but we should carefully consider the long term control of microbes and the need to have multiple tools to prevent the development of tolerances. Because microbes develop better under warm conditions, this scenario is more problematic in the warmer countries in the South of Europe.

Scenario 4. The isothiazolinones disappear and the formaldehyde releasers remain

The isothiazolinones are essential in most products, as formaldehyde releasers are not always compatible and present gaps in efficacy.

Scenario 5. Only use active substances already listed in Annex I of BPR

This scenario is not an option for many applications as the substances available in Annex I (namely sodium benzoate and lactic acid) are not technically usable in many products and their efficacy and spectrum of activity are lower compared to the two main families of actives. It may be possible to use them in some products in some industries but the BPR imposes a limitation[7].

[7] Indeed, a prerequisite is that the biocidal product is authorised according to Article 25 of BPR via a simplified authorisation procedure. But this procedure will be hampered by conditions imposed on eligibility of products under this authorisation route in the Annex I for these substances: “Concentration to be limited so that each biocidal product does not require classification according to either Directive 1999/45/EC or Regulation (EC) No 1272/2008.” As the active substances in Annex I Cat. 1 are all classified and are in general made available as 100 % active substances, it would mean that they would first have to be de-concentrated (i.e. mixed with water) at a level that would not lead to classification, which means transport of more water, fuel consumption and CO_2 emission.

Conclusion

CEPE, FEICA, A.I.S.E. and EPDLA produce water based products that have to be preserved with effective in-can preservatives. There is a great variety of micro-organisms that can destroy our products and this requires a variety of actives, both for their efficient control and to prevent the development of tolerances. The two main families (formaldehyde releasers and isothiazolinones) are essentially needed and there is no easy substitute that can fulfil all the technical and safety requirements. A holistic approach to ensure their future availability to formulators is therefore needed.

Annex I - Overview of available actives and their technical limitations, based on current knowledge

Substance:	CAS number:	Family	Technical limitations
MBM	5625-90-1	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met;
Reaction products of ethylene glycol with paraformaldehyde (EGForm)	3586-55-8	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met;
HPT	25254-50-6	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of *Pseudomonas* met; discoloration
Oxazolidin / MBO	66204-44-2	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met; limited performance
Sodium N-(hydroxymethyl)glycinate	70161-44-3	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
TMAD	5395-50-6	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
THPS	55566-30-8	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
CTAC	4080-31-3	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
HHT	4719-04-4	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of *Pseudomonas* met; discoloration
DMDMH	6440-58-0	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
EDHO	7747-35-5	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
cis CTAC	51229-78-8	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
(benzyloxy)methanol	14548-60-8	CH2O adduct	CH2O has limited activity on moulds and yeasts, some tolerances of Pseudomonas met
BIT	2634-33-5	isothiazolinone	intrinsically ineffective on Pseudomonas, *very oxidant unstable*
Mixture of CMIT/MIT 3:1	55965-84-9	isothiazolinone	use limited to 15 ppm to avoid classification, some *Pseudomonas* tolerances met at this concentration level
MIT	2682-20-4	isothiazolinone	weak against fungi but very good on bacteria including *Pseudomonas*
OIT	26530-20-1	isothiazolinone	good fungicide, limited bactericide
BBIT	4299-07-4	isothiazolinone	short shelf life
DTBMA	2527-58-4		Can in certain matrices degrade to MBIT, which is an isothiazolinone
IPBC	55406-53-6		limited antibacterial activity, intrinsically ineffective against Pseudomonas, good fungicide; chemically unstable, risks of discoloration
Bronopol	52-51-7		does not act as CH2O releaser, acts on its own but releases formaldehyde by degradation of parent compound; high concentration needed, chemically very unstable, risks of discoloration
Zinc pyrithione	13463-41-7	pyrithione	Needs high concentration; limited antibacterial activity, intrinsically ineffective against *Pseudomonas,* very oxidant unstable, risks of discoloration
2-Phenoxyethanol	122-99-6	phenol	Overall limied activity, very limited against bacteria, ineffective on *Pseudomonas,* smells, VOC, very high concentration needed
Formic acid	64-18-6	acid	limited performance, pH and odour issues
Dazomet	533-74-4		short shelf life (hydrolysis in water)
DBDCB	35691-65-7		short shelf life in comb. with nucleophilics, alone weak performance, suitable in combinations e.g. BIT for some applications
L-(+)-lactic acid	79-33-4	acid	limited performance, pH issue
Hexa-2,4-dienoic acid / Sorbic acid	110-44-1	acid	limited performance, pH issue
Potassium Sorbate	24634-61-5		limited performance, requires high concentration, which loads salt
DBNPA	10222-01-2		short shelf life, used for very short term treatment (such as raw materials) but not for shelf life preservation.
Biphenyl-2-ol	90-43-7	phenol	phenol, gives smell; high concentration needed, very weak bactericide, intrinsically ineffective against *Pseudomonas* , limited availability in the water phase, migrates into polymers/plastics
Sodium 2-biphenylate	132-27-4	phenol	phenol, gives smell, limited uses
Dodecylguanidine monohydrochloride	13590-97-1		incompatible, surface active
Potassium 2-biphenylate	13707-65-8	phenol	phenol, gives smell, limited uses
Peracetic acid	79-21-0	acid	short shelf life, pH and high reactivity issues
Glutaraldehyde	111-30-8		short shelf life. Also can cause cross link reactions hence technical incompatibility, destroys enzymes
Hydrogen peroxide	7722-84-1		short shelf life
Chlorocresol	59-50-7	phenol	phenol, gives smell
Sodium p-chloro-m-cresolate (Covered by chlorocresol)	15733-22-9	phenol	phenol, gives smell
PHMB	27083-27-8 / 322		incompatible, surface active, low efficacy
DDAC	7173-51-5		incompatible, surface active
Quaternary ammonium compounds, di-C8-10-alkyldimethyl, chlorides (see DDAC)	68424-95-3		incompatible, surface active
Diamine	2372-82-9	amine	incompatible, surface active, low efficacy
Silver chloride adsorbed to titanium dioxide (initially notified under silver chloride)			limited performance; very limited against moulds and yeasts, relative high concentrations needed, expensive, risks of discoloration
Sodium pyrithione	3811-73-2	pyrithione	limited performance
Silver chloride	7783-90-6		limited performance; very limited against moulds and yeasts, relative high concentrations needed, expensive, risks of discoloration
p-[(diiodomethyl)sulphonyl]toluene	20018-09-1		can cause discoloration, limited uses

NB The present table has been compiled based on the best of our formulators' knowledge. It should be kept in mind that we do not cover all producers in the European market, and while the present information has been put together in good faith, it cannot be regarded as totally exhaustive and complete. For additional technical expertise, we would suggest to contact the biocides suppliers.