STATEMENT – ESSENTIALITY OF CHLOROPHENE

The biocidal active substance chlorophene is classified for carcinogenicity category 2 and reproductive toxicity category 2 according to Regulation (EC) 1272/2008. Pending of the adoption of EU criteria for endocrine disruptors (ED) substances fulfilling this classification are considered as having endocrine-disrupting properties (interim ED criteria) and shall not be approved for uses acc. Biocidal Products Regulation (EU) 528/2012 (BPR).

The eCA Norway has thus proposed the non-approval for chlorophene in the context of BPR. However, it is acknowledged that the interim ED criteria may lead to false positive or false negative results when trying to identify endocrine disruptors. The EU rule makers are aware of the short-comings of the interim criteria and thus these will be replaced within short.

It is also today not appropriate to base an approval decision on the interim criteria. Nevertheless, with this statement we want to inform you about the need for chlorophene as tool for the management of disease prevention.

Chlorophene is supported as active substance for biocidal applications in product types 2 (disinfection of surfaces, materials, equipment and furniture) as well as for product-type 3 (veterinary hygiene) of the BPR. The substance is intended to be used as a heavy-duty disinfectant which includes disinfection of surgery rooms and infectious disease wards as well as small-area disinfection of objects as washbasins and toilet facilities. It was found efficacious against different fungi and bacteria amongst which are *Escherichia coli*, *Pseudomonas aeruginosa*, *Aspergillus* species and *Mycobacteria*.

Fungal or bacterial infections may lead to severe health threats, among them aspergillosis and tuberculosis. Disinfection is becoming increasingly important due to resistance development against medical treatments while at the same time only limited research is undertaken to investigate new medical treatments against such infections.

A standard formulation (SF) containing 10% Preventol® BP (contains >=95% Chlorophene) was tested for efficacy against mycobacteria in accordance with the European norms EN 14204 (“Quantitative suspension test for the evaluation of mycobactericidal activity of chemical disinfectants and antiseptics used in the veterinary area”) and EN 14348 (“Quantitative suspension test for the evaluation of mycobactericidal activity of chemical disinfectants and antiseptics used in the medical area including instrument disinfectants”).

In the EN 14204 test the standard formulation containing 10% Preventol® BP showed mycobactericidal activity for the strain *Mycobacterium avium* at a concentration of 1.5% (which corresponds to ca. 0.15 % chlorophene) with a 60 minutes contact time at 10°C and with simulated low level soiling conditions [1].

In the EN 14348 test the standard formulation containing 10% Preventol® BP showed mycobactericidal activity for the strain *Mycobacterium avium* and *Mycobacterium terrae* at a concentration of 0.25 % (which corresponds to ca. 0.025 % chlorophene) with a 60 minutes contact time at 20°C and with simulated low level soiling conditions [2].

Furthermore, for *Mycobacterium terrae*, the minimal inhibitory concentration was determined to 0.01% chlorophene [3].

Mycobactrium terrae is the surrogate for establishing tuberculocidal activity. Therefore it is recommended to use this species for determining the tuberculocidal activity of products. If a product passes the test with *Mycobacterium terrae,* the product can be characterized as possessing tuberculocidal activity. Chlorophene passed the tests against *Mycobacterium terrae* and can be thus considered as effective against *Mycobacterium tuberculosis* [4,5].

According to World Health Organization (WHO) the infectious disease Tuberculosis (TB) caused by *Mycobacteria tuberculosis* has existed for thousands of years and remains as a major global health problem. In the EU 484,733 TB cases have been notified in 2015. Among them a total number of 19,000 cases has been reported with estimated multiple drug resistance. More than 4000 cases with resistance have been confirmed in the laboratory (MDR/ RR-TB: 4 081, XDR-TB: 117[1])[6].The infection with *Mycobacteria tuberculosis* may lead to fatalities in the absence of adequate and efficient treatment measures which necessarily include both medical treatment and appropriate disinfection procedures for prevention of the spreading out of the pathogens, especially in health care units.

Other mycobacteria species such as *Mycobacterium bovis*, *Mycobacterium avium* subsp. *avium*, *Mycobacterium avium* subsp. *paratuberculosis*, *Mycobacterium ulcerans* may cause diseases to a wide range of animal species [7] . For example Bovin tuberculosis caused by *Mycobacterium bovis* is a chronic bacterial disease of cattle and is distributed with a high prevalence in the cattle populations of many countries worldwide. This disease is a significant zoonosis as the infection can be transmitted to human by direct contact between infected cattle and workers and their families, as well as from infected food products. Cattles are mostly infected by *Mycobactrium bovis,* but other domesticated and wild mammals can be also infected [8,9].

Avian Mycobacteriosis most commonly caused by *Mycobacterium avium* and *Mycobacterium genavense* is an important disease which may affect companion, captive exotic, wild and domestic birds. In commercial animal production the disease can result in economic losses, such as reduced animal production. Generally, spreading of mycobacterium infections caused by *Mycobacterium tuberculosis* and *Mycobactreium bovis* could be prevented by using antibiotics, but this should be avoided, due to possible occurrence of resistance with possible impact also on human health, high treatment costs and prolonged keeping of animals. Also for the poultry sector, treatment with antibiotics is no good option considering resistance development of *Mycobacterium avium* to antibiotics and furthermore, economic

[1] MDR is TB resistant to rifampicin and isoniazid; RR is TB resistant to rifampicin. XDR is extensively drug-resistant TB.

losses. In some countries preventive antibiotics treatment is forbidden. Consequently good biosecurity and hygiene management become even more important to reduce the risk of disease transmission to human and animals. Disinfection is one of the main biosecurity measures to control the spread of animal diseases. For this reason it is important to have a sufficient number of disinfectants based on different actives available which are efficacious against a broad range of microorganisms and to avoid the resistance development also against the disinfectants [10, 11]. In terms of Glutaraldehyde, even ECHA has recommended to use more than one product simultaneously, or to alternate treatment regimes to control the occurrence of resistance [12].

A number of active ingredients are supported for uses in the PT2 and PT3 of BPR 528/2012. However, for decision drawing on chlorophene the potential alternatives need be compared to it regarding their specific efficacy profile, technical properties, suitability of possible application techniques and occurrence of resistance. A complete picture is only available after all actives have been assessed and when efficacy data for **biocidal products** are available.

The competent authority reports have not been published for all the actives yet and BPR product authorization stage for biocidal products is just at its beginning. In the following we took available information from published competent authority reports. It turns out that overall only a limited number of actives is on the market which could be fit for purpose.

Conclusion: Chlorophene is an essential tool for disinfection management in health care units, private homes of infected persons as well as animal housing for the supported application methods. Treatment is efficacious against organisms causing diseases as tuberculosis or aspergillosis .

Table 1: Active substances evaluated under BPR in PT2 and 3. Remarks/limitations in comparison to the intended uses and application pattern of chlorophene. References: published competent authority reports for the respective active substances. https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances. Further references as cited.

Active **[CAS]**	**PT 2**	**PT 3**	**Uses**	**Remarks/Limitations**	**Possible alternative to chlorophene**
Chlorophene **[120-32-1]**	Yes	Yes	Bactericide (eg against Mycobacteria spp), Fungicide (eg against Aspergillus spp.) Heavy duty disinfectant: disinfection of surgery rooms and disease wards, small-area disinfection of objects as washbasins and toilet facilities. Veterinary hygiene: disinfection of		

			animal housing		
5-chloro-2-(4-chlorphenoxy)phenol (DCPP) **[3380-30-1]**	Yes	No	Bactericidal uses. For use in dish washing liquids Not suitable for heavy duty applications	No fungicidal efficacy Not available for PT 3 Based on the available information it cannot be excluded that resistance and cross resistance to antibiotics may occur. vB and T met: Candidate for substitution.	No
Amines, N-C10-16-alkyltrimethylenedi-, reaction products with chloroacetic acid (Ampholyt 20) **[139734-65-9]**	Yes	Yes	bactericide, yeasticide and, a limited virucide (effective against enveloped viruses) and active against Adenovirus	No fungicidal efficacy	No
Bacillus amyloliquefaciens **[-]**	No	Yes	Control potentially harmful bacteria in livestock buildings and equipment of animal rearing facilities, e.g. for poultry and pig. The product is intended to complement but not to substitute chemical disinfection measures as a prophylactic treatment.	Not available for PT 2 No fungicidal activity Only complementary to chemical disinfection as a prophylactic treatment	No
Benzoic acid **[65-85-0]**	No	Yes	bactericide, fungicide and virucide	According to CAR the substance is efficacious under clean conditions only. A number of yeasts are known	No

				to be resistant to benzoates. Some micro-organisms have resistance to benzoates because they metabolize the compounds.	
Biphenyl-2-ol **[90-43-7]**	Yes	Yes	Broad efficacy against harmful organisms (bacteria, fungi, yeasts)		Yes
Calcium dihydroxide/calcium hydroxide/caustic lime/hydrated lime/slaked lime **[1305-62-0]**	Yes	Yes	There are four structurally related lime compounds under review. These are hydrated lime, burnt lime, hydrated dolomitic lime and burnt dolomitic lime. As they all share similar toxicological properties, in the risk assessment, where appropriate, they have been considered together. Disinfectant products based on the four lime compounds are used only by professional workers in specific treatment areas. They are used as disinfectants for the treatment of manure and other digestive tract contents (PT 3) and for the treatment of sewage sludge (PT 2). Their function is to kill viruses, bacteria and parasites present in the media to which they are applied. This is achieved through an increase in alkalinity and temperature and a decrease in water availability. The substances are applied as solids and mixed with the substrates.	Not suitable for disinfection of hard surfaces as walls. It is not possible to apply the solid on eg walls or other surfaces.	No
Calcium magnesium oxide/dolomitic lime [37247-91-9]	Yes	Yes			No
Calcium magnesium tetrahydroxide/calcium magnesium hydroxide/hydrated dolomitic lime [39445-23-3]	Yes	Yes			No
Calcium oxide/lime/burnt lime/quicklime [1305-78-8]	Yes	Yes			No
Chlorocresol [59-50-7]	Yes	Yes	Surface disinfection Efficacy against bacteria, fungi and oocysts		Yes

Citric acid [77-92-9]	Yes	No	The only intended use is impregnation of facial tissues. The applicant does not require any other use. The organisms to be controlled and claimed are Rhinoviruses 1A, Rhinoviruses 2, Respiratory Syncytial Virus (RSV), Influenza A and Influenza B.	No bactericide and/or fungicide Surface disinfection not intended. Not available for PT3.	No
Copper sulphate pentahydrate [7758-99-8]	yes	no	Bactericide Other effects not proven Copper sulfate pentahydrate is incorporated into products used with washing machines, where the presence of the Cu 2+ ion can exert a biocidal effect. The product is dosed through automatic dosing system into the rinse water of industrial washing units. The product is added after the detergent wash and before the final rinse cycle, to reduce the bacterial contamination of clothing or overalls.	Not suitable for the treatment of surfaces. Not available for PT 3	No
Glutaral (Glutaraldehyde) [111-30-8]	yes	yes	PT2: - Hard surface disinfection in hospital - Hard surface disinfection in industrial areas Target organisms: Bacteria, mycobacteria, bacterial spores, fungi (yeasts and moulds), virus, algae, biofilms PT3: - Poultry Farm Disinfection - Pig Farm Disinfection Target organisms: Bacteria, mycobacteria, bacterial spores, fungi (yeasts and moulds), virus	Resistance to glutaraldehyde in certain mycobacteria strains has been reported in hospitals. Resistant strains have grown in surgical equipment, e.g. endoscopes. Resistance against glutaraldehyde has been associated with improper uses of the disinfectant on dirty endoscopes and use of non-sterile water to rinse disinfected equipment. The recommended resistance management strategy is to vary the products used, to use more than one product simultaneously, or to alternate	Yes, but resistance reported in hospitals. It is recommended to vary the product used.

				treatment regimes and monitor occurrence of resistance.	
Hydrochloric acid [-]	yes	no	Main use is as lime scale remover. Acts against a range of Gram positive and Gram negative bacteria, common fungal species and common viral types. Supported use is as surface disinfectant for toilet bowls in private and domestic situations at an in-use concentration of 6%.	Due to corrosivity not suitable for uses on all hard surface materials. Large-scale surface disinfection is not intended Not available for PT 3	No
Hydrogen peroxide [7722-84-1]	yes	yes	PT2: Surface disinfection by VHP process in private or public hygiene disinfection of rooms using the vaporised hydrogen peroxide (VHP) process PT3: Disinfection of animal housing by spraying	In dried surface assays with various bacterial species, hydrogen peroxide always demonstrates a good bacteriostatic effect against attached bacteria, but poor bactericidal activity [11]. it is very rapidly regraded by catalase, so it is not suitable for PT3 applications where there is a much higher presence of soil. Due to the fact that hydrogen peroxide is rapidly degraded by oxidising itself all possible particles and not only bacteria or fungi, it is not suitable for the wiping and mopping application. The presence of catalase or other peroxidases in organisms can increase tolerance in the presence of lower concentrations [12].	Yes, but not all applications possible.

Iodine [7553-56-2]	no	yes	Teat disinfection Disinfection of animal houses Bactericide Viricide and fungicide effect is not proven	Not available for PT 2	PT3: Yes, but fungicidal effect is not proven PT2: No
Mixture of 5-chloro-2-methyl-2H- isothiazol-3-one (EINECS 247-500-7) and 2-methyl-2H-isothiazol-3-one (EINECS 220-239-6) (Mixture of CMIT/MIT) [55965-84-9]	yes	no	C(M)IT/MIT biocide is claimed as an antimicrobial product for the preservation of air conditioning and air washing systems, and for chemical toilets. C(M)IT/MIT may function as a bacteristat and a fungistat.	Not suitable for treatment of surfaces. Not available for PT 3	No
Nonanoic acid, Pelargonic acid [112-05-0]	yes	no	Nonanoic acid is used for remedial treatment of masonry, such as walls, facades, paths, terraces, fences or gravestones, to control an excessive development of green algae (Chlorophyta sp.) Only algaecidal effect is proven	Not intended to use it as an active substance for hard surface disinfectant against bacteria, fungi and viruses. Not available for PT 3	No
Peracetic acid [79-21-0]	yes	yes	PT2: Disinfectants and algaecides not intended for direct application to human or animals PT3: Veterinary Hygiene Bactericide, fungicide and viricide	It is very corrosive to metals and great care needs to be taken in its use [11].	Yes (but not suitable for all surfaces)
PHMB (1600; 1.8) (polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1600 and a mean	yes	yes	PT2: Bactericidal and yeasticidal Viricidal and fungicidal is withdrawn by the applicant PT3: Bactericide.	The evaluation of the literature studies provided by the applicant does not show particular resistance to PHMB with bacteria. Nevertheless it is not appropriate to conclude that PHMB resistance is not an	Yes, but there is a risk of resistance development

polydispersity (PDI) of 1.8) **[27083-27-8]**			Viricidal and fungicidal is withdrawn by the applicant	issue and that a resistance management strategy is not required. vB and T met: Candidate for substitution.	
Propan-2-ol **[67-63-0]**	Yes	No	Bactericide Efficacy against bacteria spores, fungi and viruses are not proven.	A natural resistance against sporulated bacteria is known where 2-propanol is ineffective at any concentration. Not available for PT 3	No
Polyvinylpyrrolidone iodine **[25655-41-8]**	No	Yes	Teat disinfection Disinfection of animal houses Bactericide	Not available for PT 2 Viricide and fungicide effect is not proven	No

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