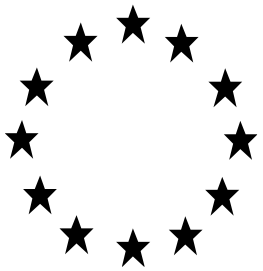
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Chlorophene

Product-type 2
(Disinfectants and algaecides not intended for direct application to humans or animals)

April 2020

Norway

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the active substance chlorophene in product-type 2 (disinfectants and algaecides not intended for direct application to humans or animals) carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012 (BPR), with a view to the possible approval of this substance.

Chlorophene (CAS no. 120-32-1) was notified as an existing active substance, by LANXESS Deutschland GmbH and Clariant UK Ldt. through The Chlorophene Task Force.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

In accordance with the provisions of Article 7(1) of that Regulation, Norway was designated as a Rapporteur to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for chlorophene as an active substance in product-type 2 was 31 July 2007, in accordance with Annex V of Regulation (EC) No 1451/2007.

On 31 July 2007, the Norwegian competent authorities received a dossier from The Chlorophene Task Force. The Rapporteur accepted the dossier as complete for the purpose of the evaluation on 1 February 2008. In a letter of 30 April 2010 Clariant UK Ldt. withdrew the application for approval of chlorophene and The Chlorophene Task Force cancelled the co-operation contract. Hence, LANXESS Deutschland GmbH is hereafter referred to as the applicant.

With the introduction of the exclusion and substitution criteria in article 5(1) and 10(1) of Regulation (EU) No 528/2012, with effect from 1 September 2013, the need for harmonised classification of active substances that might fulfil these criteria became crucial for the approval process. As chlorophene did not have a harmonised classification and the Rapporteur through the evaluation of the submitted data found that the substance might fulfil some of these criteria, a CLH dossier was submitted to the European Chemical Agency (ECHA) on 30 June 2014. This procedure was also in line with the guidance documents agreed by the CA meeting[2]. A Committee for Risk Assessment (RAC) opinion was adopted on 12 March 2015, and the active substance was included in the 10th ATP to CLP (Commission Regulation (EU) 2017/776).On 22 December 2016, the Rapporteur submitted to the Agency (ECHA) and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

[1] Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

[2] See document CA-Nov14-Doc.4.5-Final: Further guidance on the procedures related to the examination of the exclusion criteria and the conditions for derogation under Article 5(2), and document CA-Sept13-Doc.8.3–Final: Review programme of active substances: Establishment of a work programme to meet the 2024 deadline.

However, after the finalisation of the first CA-report for PT2, the eCA was informed by the US EPA that the key 90 day dog study in the dossier was deemed invalid by the US EPA as the study had been conducted at a testing laboratory having falsified data reports on several chemicals. The study was therefore not included in the Registration Review Draft Risk Assessment performed by the US-EPA. The study was also considered invalid in the EU submission. Removing the study from the dossier, resulted in a datagap for the subchronic toxicity study in the second animal species (dog).

Given that the data gap was identified at a very late stage (i.e. after the BPC discussion), the eCA suggested to apply an additional AF in the AEL setting to compensate for the incomplete data package in order to be able to finalise the risk assessment for chlorophene. The revised risk assessment was discussed at the Human Health WG V 2019) where AELmedium term og AELlong term were re-established. Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly at the BPC-34.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of chlorophene for product-type 2, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

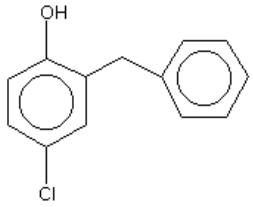
2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

Identity

CAS-No.	120-32-1	
EINECS-No.	204-385-8	
Other No. (CIPAC, ELINCS)	Not allocated	
IUPAC Name	2-Benzyl-4-chlorophenol	
CAS Name	Phenol, 4-chloro-2-(phenylmethyl)-	
Common name	Common name:	Chlorophene
	EINECS name:	Chlorophene
	Trade name:	Preventol BP
		Nipacide BCP
Synonyms	BCP	

	o-Benzyl-p-chlorophenol
	4-Chloro-alpha-phenyl-o-cresol
	5-Chloro-2-hydroxydiphenylmethane
Molecular formula	$C_{13}H_{11}ClO$
Smiles	Oc(c(cc(c1)Cl)Cc(cccc2)c2)c1
Structural formula	
Molecular weight (g/mol)	218.7 g/mol

Physico-Chemical properties

Chlorophene is a solid substance (white to slightly yellow colour) with a minimum purity of 966 g/kg. The melting point was determined to be 45.9 °C. The compound does not boil, but decomposes at 110 °C. Chlorophene has a vapour pressure below $1.0 \cdot 10^{-3}$ Pa at 20 °C and Henry's law constant of $1.87 \cdot 10^{-3}$ Pa·m^3/mol at 20 °C. The log K_{ow} for chlorophene was determined to be 4.276 at pH 4 and 25 °C, no significant change in log K_{ow} was seen with an increase in pH. The surface tension for chlorophene was determined to 57.3 mN/m at 20 °C (0.09 g/L), which means that chlorophene is surface active. The solubility was measured to be above 250 g/L in toluene at 10, 20 and 30 °C. The water solubility was determined to be 0.083, 0.117 and 0.199 g/L at 10, 20 and 30 °C, respectively. Chlorophene was not deemed as flammable, oxidizing or explosive. Chlorophene has no auto flammability up to its melting point.

Methods of Analysis

The active substance chlorophene was determined in technical produced material by a validated HPLC-DAD method. Impurities were determined by ESI-MS detection. External standards were employed for quantification. The identity of the impurities is given in the confidential annex.

Acceptable and validated analytical methods based on HPLC-MS for the determination of chlorophene residues in water are available. External standards were used for all sample matrices, which may cause interference in complex samples like soil samples. The quantification limits were set to 0.01 mg/kg, 0.3 µg/m^3 and 0.1 µg/L for soil, air and water, respectively. Fully validated confirmatory methods for determination of chlorophene in soil and air are to be submitted as soon as possible, but no later than 6 months before the date of approval to the evaluating Competent Authority (NO).

Analytical methods for the determination of chlorophene residues in animal and human body fluids and tissues were not submitted, as the active substance is not classified as toxic or highly toxic.

Analytical methods for the determination of chlorophene residues in/on food and/or feedstuffs were not submitted. For use in PT 2, the contamination of food and/or feedstuffs is not anticipated and an analytical method was therefore not required.

2.1.1.1. The biocidal product

The representative biocidal product is an emulsifiable concentrate containing 5% chlorophene in addition to 3 other active substances. For use in product-type 2 (PT 2), the representative biocidal product is intended to be diluted 56-fold with water to obtain the recommended in-use concentration of 0.09 % chlorophene. During the peer review process, the applicant indicated that also ready to use products (RTU) could be formulated and placed on the market.

2.1.2. Intended Uses and Efficacy

Chlorophene is a multi-site bactericide and fungicide with basic activity at the cell wall, disruption of membrane potentials and general membrane permeability of the cytoplasmic membrane. Chlorophene adsorbs to the cell membrane, following which the function of membrane proteins is disturbed, and substrate transport and ATP synthesis are inhibited. The cell membrane loses its semi-permeability and ions and organic molecules escape.

The active substance chlorophene is intended to be used as a heavy-duty disinfectant for both professional and private use. Professional use includes disinfection of surgery rooms and infectious disease wards as well as small-area use for disinfection of objects as washbasins and toilet facilities in hospitals by professional cleaning personnel. Private use of chlorophene is also limited to disinfection of objects, such as washbasins and toilet facilities. Professional users may be expected to use chlorophene-containing products on a daily basis, while non-professional use occurs more rarely, presumably on a weekly basis.

In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

As part of the documentation of the antimicrobial activity of chlorophene, minimum inhibitory concentrations (MICs) for bacteria, mycobacteria and fungi were established, which indicate that the substance has a broad antimicrobial spectrum. Furthermore, the assessment of the biocidal activity of chlorophene demonstrates that it has a sufficient level of efficacy against the target organism(s) which are bacteria and fungi. The evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

For the active substance chlorophene, efficacy towards bacteria has been demonstrated according to EN 1276 / EN 1650. The chlorophene concentrations needed for bactericidal activity range from 0.1 % (*Escherichia coli*, *Staphylococcus aureus* and *Enterococcus hirae*, 10 minutes contact time, low protein load) to > 3 % (*Pseudomonas aeruginosa*, 10 minutes contact time, high protein load). The concentrations needed to achieve fungicidal activity range from 0.25 % (*Candida albicans*, 10 minutes contact time, low protein load) to > 5 % (*Aspergillus niger*, 10 minutes contact time, high protein load).

Efficacy towards mycobacteria has also been demonstrated for the active substance according to DIN EN 14204:2012. The chlorophene concentration needed for mycobactericidal activity was 0.15 % (*Mycobacterium avium,* 60 min contact time, low protein load)

The evaluated representative biocidal product is also shown to have bactericidal and fungicidal activity according to EN 1276 / EN 1650. In the product, the active substance chlorophene is combined with three other biocidal active compounds. The concentrations of the representative biocidal product needed for bactericidal activity range from 0.1 % (*E. coli*, *S. aureus* and *E. hirae*, 10 minutes contact time, low protein load) to 1.0 % (*P. aeruginosa*, 10 minutes contact time,

high protein load). The concentrations needed to achieve fungicidal activity range from 0.25 % (*C. albicans*, 10 minutes contact time, low protein load) to 1.0 % (*A. niger*, 10 minutes contact time, high protein load).

Due to the unspecific mode of action (multi-site activity), the development of resistance towards chlorophene has not been observed and is not expected.

2.1.3. Classification and Labelling

Harmonised classification [10th ATP to CLP (Commission Regulation (EU) 2017/776].

Pictogram:	
Signal word:	Danger
Classification:	Carc. 2 Repr. 2 Acute Tox. 4 Skin Irrit. 2 Skin Sens. 1 Eye Dam. 1 STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1
H-Statements:	H351 Suspected of causing cancer H361f Suspected of damaging fertility H332 Harmful if inhaled. H315 Causes skin irritation. H317 May cause an allergic skin reaction. H318 Causes serious eye damage. H373 May cause damage to kidneys through prolonged exposure H400 Very toxic to aquatic life. H410 Very toxic to aquatic life with long lasting effects.
M-Factor (for environmental classification):	M=1 (Acute) M=100 (Chronic)

2.1.3.1. Proposal for classification and labelling of the representative biocidal product

The proposed classification of the representative biocidal product according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation) is shown in the table below. The proposal is based on results from the studies with the representative biocidal product and the classification and concentration of the ingredients in the product. This includes the classification of chlorophene given in the 10th ATP to CLP (Commission Regulation (EU) 2017/776).

Hazard pictograms	
Signal words	Danger
Hazard class and categories	Flam. Liq. 3, Acute Tox.4 Skin Corr. 1A Skin Sens 1 STOT SE 3 Carc. 2 Repr. 2 Aquatic chronic 1
Hazard statements	H226 Flammable liquid and vapour H302 Harmful if swallowed H312 Harmful in contact with skin H314 Causes severe skin burns and eye damage H317 May cause an allergic skin reaction H336 May cause drowsiness and dizziness H351 Suspected of causing cancer H361f Suspected of damaging fertility H410 Very toxic to aquatic life with long lasting effects *Supplemental hazard information to be put on the label:* EUH071 Corrosive to the respiratory tract
Precautionary statements	As the representative biocidal product is only an example product for evaluating chlorophene as an active substance under the biocidal review programme and the product is not currently on the European market, the precautionary statements have not been included in this table.

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

2.2.1.1. Hazard identification and effects assessment

Toxicology hazard summary

Toxicokinetics and metabolism

In an ADME study of chlorophene in rat, oral administration of chlorophene resulted in higher relative percentages of chlorophene excreted in the faeces compared to i.v. administration. After dermal application, a high percentage of the total dose of chlorophene was present at the application site at the end of the study. These findings indicated that chlorophene was incompletely absorbed through both GI and skin. Levels in bile were not measured after oral administration, and the oral absorption could be estimated based on the lowest urine excretion in addition to the chlorophene levels found in the tissues. As this assumption is assumed to be too conservative, the oral absorption was estimated by comparing the oral and i.v. administration of test substance (measurement of net test substance present in urine plus

expired air plus carcass by each of the two routes). An oral absorption of 70 % for chlorophene was concluded upon based on this comparison (used in the AEL-setting).

Chlorophene was rapidly distributed to tissues. Most of the administered chlorophene was excreted and the tissue levels were generally low at 3 days after exposure (with the only exception at the application site in the dermal exposure group). However, the highest concentration of chlorophene-derived radioactivity was found in the kidney during the whole measuring period. This affinity of renal tissue for chlorophene is likely to play a role in the suggested nephrotoxicity of this compound. In addition, the studies indicated that enterohepatic circulation was involved in chlorophene disposition. The major excretion route after oral and dermal absorption of chlorophene was via faeces.

The major *in vivo* metabolites detected after chlorophene exposure were glucuronyl conjugates of chlorophene and 4-hydroxy-chlorophene in faeces and urine. Glutathione conjugates were also found in urine.

Based on the levels in urine, faeces and tissues, dermal absorption of chlorophene was approximately 62 % in a study where a 4 % of chlorophene dissolved in acetone was tested. In another study where a water diluted commercial 5 % disinfectant solution was used (test concentrations of 0.05 %, 0.5 % and 5 %), the highest measured dermal absorption value was 60 %. A dermal absorption value of 60 % was decided to be used for the in use concentration of the example product (0.09 %) in the PT 2 CAR for chlorophene. However, a default dermal absorption value of 100 % was decided to be used for the concentrate due to the corrosive properties of the example product in the PT 2 CAR. For product authorisation, the applicability of the test available must be decided and possible further information may be requested. In addition, at WGIII 2017 (Ad hoc follow up) it was decided that a dermal absorption value of 60 % should be used to assess exposure to dried residues of chlorophene (in accordance with EFSA guidance on dermal absorption, 2012).

Acute health effects

Chlorophene is of low toxicity by the oral (LD_{50} = 3852 mg/kg) and percutaneous route (LD_{50} > 2000 mg/kg), and of moderate toxicity via inhalation (LC_{50} = 2.43 mg/L/4h). The LC_{50} value of 2.43 mg/L/4h is > 1 but < 5 (dust/mist), and meets the criteria for classification in category 4.

Irritant effects of chlorophene were tested on the skin and eyes of rabbits. It caused strong irritation on the skin with strong erythema and oedema. All studies were performed according to OECD guideline 404. The overall results show that the substance fulfils the criteria for classification as a skin irritant (Skin Irrit 2; H315: Causes skin irritation). Chlorophene also caused significant irritation of the eye in tests on albino rabbits. Lesions of cornea and iris as well as conjunctival redness and chemosis, all of which persisted until the end of the observation period, were noted. Therefore, the EU criteria for classification as a severe eye irritant are met (Eye Dam. 1; H318: Causes serious eye damage).

Chlorophene was tested for its skin sensitisation potential in several tests on Guinea pigs. Human data from clinical tests in people already sensitised were also submitted. In conclusion, results from three positive Buehler tests provided collectively a sufficient basis for classifying chlorophene as a skin sensitizer even though they had some shortcomings. Human data from clinical tests also showed that chlorophene has potential to elicit skin sensitisation reactions in people. However, due to deficiencies in the animal studies (including choice of test concentration) and few human data (all with limitations), neither the animal nor the human studies could be used for further sub categorisation into category 1A or 1B. Hence, chlorophene should be

classified as Skin Sens. 1, H317: May cause an allergic skin reaction.

Repeated-dose toxicity

The repeat dose toxicity of chlorophene via the oral route has been investigated in rats (16 days - 2 years) and mice (16 days - 2 years). Dermal toxicity studies have been performed in rabbits (5 days - 4 weeks). There are no studies in experimental animals that address the repeated dose toxicity of chlorophene by the inhalation route.

In the repeated dose studies, the kidneys were the observed target organ in all species, and effects such as increased kidney weights, histopathological changes, kidney lesions and nephropathy were seen.

On the basis of increased incidence of nephropathy and increased kidney weight at relevant doses in rodents after oral administration, and in rabbits after dermal administration of chlorophene, chlorophene should be classified as STOT RE 2, H372: May cause damage to kidneys through prolonged exposure.

Other effects seen at higher doses and or longer exposure time (rat, mouse) were increased absolute and relative liver weight and reduced body weight gain. Local reactions to treatment (e.g. erythema, oedema and discolouration of the skin) were observed in all the dermal toxicity studies with rabbit.

Genotoxicity

In vitro, the conclusion on the genotoxicity was equivocal. The test requirements were met with an *in vitro* test for gene mutations in bacteria, an *in vitro* cytogenicity test in mammalian cells and an *in vitro* gene mutation test in mammalian cells. Several of the *in vitro* studies exhibit study insufficiencies that reduce their power to conclude that chlorophene is not genotoxic. In two independent *in vitro* mutagenicity studies in mammalian cells (mouse L5178Y cells), assessing mutagenesis in two different loci (HPRT and TK), there were indications of increased mutation frequencies without metabolic activation. The first study is a well-conducted study following OECD Guideline 476 (from 1997), and the latter study is a non-guideline, non-GLP $TK^{+/-}$ assay conducted with chlorophene of unknown specification.

In the case of positive or equivocal results in *in vitro* tests, appropriate *in vivo* genotoxicity studies shall be considered. For chlorophene, there were equivocal results in two mouse lymphoma studies. They were followed up with *in vivo* studies. There were no indications of clastogenicity or aneugenicity in the *in vivo* micronucleus assay in mice. In order to cover potential gene mutation induction, the applicant agreed to conduct a second *in vivo* genotoxicity assay (*in vivo* comet assay) in mice. However, the target organ (the kidney) was not included, hampering a conclusion on the potential genotoxic properties of chlorophene in relevant tissues. Data from liver could act as a metabolically active surrogate tissue. No genotoxicity was observed in liver at the highest dose tested (360 mg/kg bw, MTD), and the test was considered negative. A dominant-lethal test, only available as a summary, reported a negative result.

In summary, several of the key studies exhibit study insufficiencies (some minor, others more critical) that impede establishment of solid conclusions on genotoxicity. But, based on an overall evaluation of the available data using a Weight of Evidence approach, the decision on genotoxicity is negative. There were no positive findings in bacterial tests, no clear induction of genotoxicity or mutagenicity in any test, only equivocal results with no clear dose-response

relationships, and often occurring at doses with significant cytotoxicity. *In vivo*, there were no indications of genotoxicity in the tests provided. In the absence of any clear positive results, and given the range of tests conducted, no germ cell mutagenicity classification for chlorophene is justified.

Carcinogenicity

The carcinogenicity of chlorophene was investigated in two-year gavage studies in rats and mice. In addition, as supportive information, a non-guideline dermal initiation/promotion study in mice and a short-term dermal carcinogenicity study in transgenic mice were also evaluated. The two dermal cancer studies were, however, according to RAC of limited relevance and reliability (both with limited reporting and a lack of histopathological analysis, and the assays may have been compromised by the application of doses that were significantly irritant to mouse skin).

In female F344 rats, single incidences of a rare renal tumour type occurred in the mid and top dose groups. Renal transitional cell carcinomas are extremely rare in historical reference data. None of the tumours found in male rats could be ascribed as an effect of the test substance. The rarity of this tumour type raises concern, since the tumour occurred twice in this study, which reduces the possibility that the tumours occurred by chance. The tumour type (Transitional cell carcinoma, TCC) is in addition relevant for humans. There was, however, no mechanistic basis to suggest that the TCC in female rats in this study was treatment related. There was no evidence of chlorophene being genotoxic, and no clear relationship was established between treatment-related toxicity (e.g. renal transitional cell hyperplasia) and susceptibility of animals to this tumour type. The evidence for a carcinogenic effect of chlorophene in female rats was therefore weak, but it could not be disregarded completely. Hence, the TCC occurrence should be included in the overall evaluation of the carcinogenicity of chlorophene. Nephropathy was also seen in this study where the severity was significantly increased in a time- and dose-dependent manner both in males and females, with males as the most sensitive sex.

In the two-year carcinogenicity gavage study in B6C3F1 mice, renal tubule adenomas were observed in male mice, dose-dependently across all study groups, reaching statistical significance at high dose. Renal tubule carcinoma was evident in two males at mid dose and in one male at high dose. The incidence of adenoma and carcinoma combined reached statistical significance at mid- and high dose. Renal tubular hyperplasia was also observed in all treated groups, but in the absence of a dose-response relationship. These effects were observed at doses all greater than the maximum tolerated dose (MTD) with reductions in body weight of 20, 26 and 32 % at necropsy for low-, mid- and high-dose group, respectively. However, this level of toxicity should not detract from the conclusions on carcinogenicity arising from the findings. In addition, there was no mechanistic basis to disregard the potential relevance of these tumour findings to humans. Hence, the association between renal tumours and exposure to chlorophene provides limited evidence of carcinogenicity. No neoplasms were observed in female mice. Nephropathy was also seen in this study where the severity was significantly increased in a time- and dose-dependent manner both in males and females, with males as the most sensitive sex.

In conclusion, the rare transitional cell carcinoma observed in female rats and the renal neoplasms occurring in male mice fulfil the criteria for classification of chlorophene as Carc. 2. This is also supported by the lack of a mode of action that would dismiss the relevance to humans. Chlorophene should be considered as Carcinogen category 2, H351 suspected of causing cancer.

Toxicity for reproduction; developmental toxicity and effects on fertility

Several oral developmental toxicity studies were performed in the rat. Maternal and foetal body weight gain was the affected parameters (no adverse effects on foetal development was observed). The developmental toxicity studies in rabbits did not reveal any adverse effects on foetal development at the highest dose tested (MTD was not achieved in the key study; death and bw reduction were seen in dams in other studies at higher doses than the ones tested in the key study). A limitation of these teratogenic studies (rat and rabbit) was that the dams were only exposed to chlorophene during organogenesis and not from implantation and all the way through the gestation as required in the current version of OECD guideline 414 (2001).

Two studies examining fertility and sexual function and one follow up study on lactation, all in rats, were submitted. Due to insufficiencies in the study design of both the one-generation and lactation study, the two-generation study was chosen as the key study for fertility. The two-generation reproduction oral gavage study in rats is recently performed (2008), and it confirmed that the kidneys are the target organ of chlorophene in rats. A reduction of body weight gain during gestation was observed in dams and pups of both generations in the mid and high dose. A significantly lower female fertility index was observed in both the P (high dose) and F1 (mid and high dose) generation. A significantly increased oestrous cycle length and reduced fecundity were observed in the F1 dams (high dose). No marked systemic toxicity was observed at these doses. On the basis of dose-related changes to fertility index observed in female rats treated with chlorophene (reproducible in both P and F1 generations), occurring in the absence of marked systemic toxicity and to an extent that was outside of the relevant historical control range, RAC concluded that chlorophene should be classified Repr Cat 2, H361f: Suspected of damaging fertility.

Neurotoxicity

Chlorophene bears no structural similarity to organophosphates, carbamates or other known inducers of delayed neurotoxicity. Acute and repeated-dose studies in several species did not reveal the potential for neurotoxic effects, and the rapid excretion of chlorophene precludes an accumulation of the compound.

Human data

Medical surveillance of manufacturing plant personnel involved in chlorophene production revealed no health complaints associated with potential exposure to chlorophene.

A single report of contact dermatitis from chlorophene exposure is reported in the literature. A 49-year old bar manager developed contact dermatitis against chlorophene from a glass cleaning product.

Critical endpoints and AEL derivation

Acute AEL

Findings seen in pregnant rabbits and rats (reduced bodyweight and food consumptions) were considered most relevant for establishing an acute AEL. A NOAEL in rabbit of 100 mg/kg bw/day and NOEALs in rat of 100 mg/kg bw/day and 75 mg/kg bw/day (two different studies, different dose spacing) were established. An overall NOAEL of 100 mg/kg bw/day was concluded upon and by using an Assessment Factor of 100 (inter- and intraspecies factors of 10) and an oral absorption value of 70 % an **AEL_{acute} of 0.7 mg/kg bw/day** was established.

Medium term AEL

Several studies could be relevant for establishing the medium term AEL for chlorophene as effects on kidney (target organ) were seen in all relevant studies: a dermal study in rabbit and oral gavage studies in rat.

Some of the NOAEL in the AEL-relevant studies were based on extrapolation from LOAEL to NOAEL. Based on this, BMD calculations were requested by one member state in an e-consultation launched for chlorophene (summer 2019). The eCA also considered that this assessment would contribute with meaningful information, and the BMD calculations were performed by the eCA for studies where additional information could be useful. The European Food Safety Authority guidance on the use of the benchmark dose approach in risk assessment was used (EFSA, 2017). All the BMD calculations were performed, using the EFSA web-tool for BMD analysis (R-package PROAST, version 67.0).

In the 95 days gavage study on Fisher rats a LOAEL of 120 mg/kg bw/day was established based on dose-related significantly increased incidence of nephropathy. A NOAEL of 60 mg/kg bw/day was established in this study. The bench mark dose approach resulted in a $BMDL_{5\%}$ of 40 mg/kg bw/day based on an increased relative kidney weight in males.

In the 2-generation study, male Wistar rats of the parent generation (P generation) were exposed to chlorophene for at least 15 weeks corresponding to ~105 days. Treatment-related kidney effects (e.g. nephropathy or dilated tubules) in Pmales were observed in this study at ≥ 60 mg/kg bw/day and resulted in a LOAEL of 60 mg/kg bw/day. Based on this, a NOAEL of 20 mg/kg bw/day could be established, using an extra assessment of 3 to extrapolate from LOAEL til NOAEL. The BMD calculation resulted in a $BMDL_{10\%}$ value of 74 mg/kg bw/day based on kidney dilated tubules or nephropathy and a $BMDL_{5\%}$ value of 78.8 mg/kg bw/day based on relative kidney weight in Pmales.

The BMD calculations imply that the LOAEL to NOAEL extrapolation in the 2 generations study might be too conservative. Hence, the NOAEL of 60 mg/kg bw/day in the 95 days rat study was considered more appropriate and agreed at HH WG V 2019 to be used when deriving the $AEL_{medium\ term}$.

The lowest relevant NOAEL from the most sensitive species should be used. Based on the available data, it cannot be concluded whether rat is the most sensitive species. Hence, to ensure that the AEL values are sufficient protective, an additional AF was proposed.

An assessment factor of 2 to compensate for the incomplete data package (lacking subchronic/chronic study in a non-rodent species due to the invalidation of the originally submitted 90 day dog study) was agreed at WG (HH WG V 2019) when the AEL values (medium term and long term) were re-establishing.

By using the NOAEL of 60 mg/kg bw/day, a total AF of 200 (inter- and intra-species factor of 10x10 and an AF of 2 to compensate for the lacking information on the second species) and correcting for an oral absorption of 70 %, an **AEL $_{\text{medium-term}}$ of 0.21 mg/kg bw/day** was established.

Long term AEL

In a two year study in rat a chronic LOAEL of 30 mg/kg bw/day for chlorophene was set based on nephropathy and increased kidney weight observed in male rats. By using a factor of 3 for extrapolating from LOAEL to NOAEL, a NOAEL of 10 mg/kg bw/day could be established in this rat study.

However, when the eCA used the BMD method a $BMDL_{05}$ of 7 mg/kg bw/day based on increase in relative kidney weight was calculated. The BMD value verifies that the extrapolated NOAEL of 10 mg/kg bw/day is a reasonable reference point for the AEL $_{\text{long term}}$ setting. It was agreed at HH WG V 2019 to use the extrapolated NOAEL of 10 mg/kg bw/day in the AEL $_{\text{long term}}$ derivation. By using this value, a total Assessment Factor of 200 (inter- and intraspecies factor of 10x10, and an additional factor of 2 due to the lacking information on the second species) and correcting for an oral absorption of 70 %, an **AEL long term of 0.035 mg/kg bw/day** was derived.

Table 2.1: Summary of acceptable Exposure level values (AEL)

	Value [mg/kg bw/day]	**Study**	**NOAEL / LOAEL** [mg/kg bw/day]	**AF**
AEL $_{\text{acute}}$[1]	0.7	Developmental studies in rat and rabbits	NOAEL: 100	100 (inter- and intraspecies factors 10)
AEL $_{\text{medium term}}$[1]	0.21	95 day rat study	NOAEL: 60	100 (inter- and intraspecies factors 10) and 2 (lacking information on the second species)
AEL $_{\text{long term}}$[1]	0.035	Two year study in rat	NOAEL: 10	100 (inter- and intraspecies factors 10) and 3 (extrapolating from LOAEL to NOAEL) in the rat study and 2 (lacking information on the second species)

[1] Corrected for oral absorption (70 %)

2.2.1.2. Exposure assessment

General

The active substance chlorophene (2-benzyl-4-chlorophenol) is intended to be used as a heavy-duty disinfectant for both professional and private use. Professional use includes disinfection of surgery rooms and infectious disease wards as well as small-area use for disinfection of objects

as washbasins and toilet facilities in hospitals by professional cleaning personnel and to some extent professional health care workers. Private use of chlorophene is also limited to disinfection of objects, such as washbasins and toilet facilities. Professional users may potentially use chlorophene-containing products on a daily basis, while non-professional use occurs more rarely, presumably on a weekly basis.

The exposure assessment for all use patterns is based on the representative biocidal product (5 % chlorophene w/w), which has to be diluted 56-fold with water before application. The applicant has, however, indicated in the peer review process that ready-to-use formulations with chlorophene could be the relevant formulation to be marketed in the future.

The exposure to the representative biocidal product was assessed using a tiered approach as described in the user guidance to the TNsG 2002 (2004) and in the Human TNsG on Human Exposure to Biocidal Products 2007, including the ConsExpo Web computer program.

Production/formulation of the active substance and the biocidal product

The production/formulation process of the active substance and the biocidal product is outside the scope of the Biocidal Products Regulation. The relevance of the recommendations, e.g. the personal protection equipment, must be evaluated in accordance with the directives on the protection of workers from the risks related to chemical, physical and biological agents at work and the provisions in the worker protection directives are minimum rules.

Exposure assessment for professional users

Cleaning and disinfection in hospitals is performed by professional cleaning personnel and to a lesser extent by professional health care workers. Exposure through dermal contact and through inhalation takes place during mixing (diluting the concentrated product in a bowl, bucket or bottle) and during application of the product. Application is mainly performed by wiping smaller surfaces and objects with a cloth. The oral route is excluded since it is assumed that exposure via this route will occur only by accident.

As the representative biocidal product is classified as corrosive to skin (Skin corr 1A; H314) a dermal absorption of 100 % is assumed for dermal exposure to the concentrated product. As the product is to be diluted 56-fold with water, dermal exposure from the concentrated product cannot be excluded. The model used to assess exposure from the application process includes mixing and loading. It was however necessary to add an additional mixing and loading scenario in order to apply a different dermal absorption value for this task. In line with HEADhoc recommendation 6 (2015), Mixing&loading model 2 (TNsG 2002, part 2) was used to assess exposure during mixing and loading of the product.

Exposure during application for professional users was assessed using the scenario *Professional operator diluting and mixing disinfectant and wiping surfaces using a wrung cloth,* defined in the user guidance to the TNsG 2002 (2004, p 27). The model is also included in the TNsG 2007 (TNsG 2007, p. 67).

In the HEAdhoc recommendation 2 (HEAdhoc 2014), agreed upon at WG II in March 2014, a recommended work duration of 330 minutes for professional use of PT 2 products was agreed. This task consists of 220 minutes wiping and 110 minutes of mopping. Taking into account the described limited area of use for chlorophene (heavy-duty disinfection only), with a daily consumption of 5 litres of product per hospital reported by the applicant, it was found reasonable to assume a worst-case daily work duration for professional cleaning personnel of 220 minutes.

For professional health care workers, a worst-case work duration of 120 minutes was used.

Tier 1 assumptions: In a first tier, 100 % clothing penetration was assumed. Since the TNsG model only reports hand exposure inside gloves, this figure was multiplied with 100 to simulate the absence of gloves with a mitigation factor of 90-99% (HEEG opinion 2 2008). Dermal penetration was assumed to be 100 %. To estimate exposure through inhalation, the recommended value from the User guidance to TNsG 2002 was used.

Tier 2 assumptions: To estimate body exposure, a clothing penetration of 20 % through coated coveralls was assumed for professional cleaning personnel. For the health care personnel, cotton work wear with a penetration of 50 % was assumed. (TNsG 2007; HEEG opinion 9 2010). Exposure to the hands is given as exposure inside gloves (actual hand exposure) in the TNsG model. The dermal absorption of the diluted solution was set to 60 %. Further, the exposure through inhalation was refined by applying the saturated vapour concentration at 20°C of chlorophene of 8.97E-2 mg/m^3.

The estimated exposures are presented in table 2.2.

Table 2.2: Exposure to professional users

Exposure scenario		Inhalation uptake (mg/kg b.w./day)	Dermal uptake (mg/kg b.w./day)	Total uptake (mg/kg b.w./day)
Professional users Mixing&loading model 2 (TNsG 2002) 100% dermal absorption	**Tier 1** No gloves	-	2.67×10^{-3}	2.67×10^{-3}
	Tier 2 Gloves	-	2.67×10^{-4}	2.67×10^{-4}
Professional cleaning personnel Surface disinfection model 1/3 User Guidance to TNsG 2002 (2004, p. 27)	**Tier 1** no PPE, 100 % penetration of clothing, 100 % dermal absorption	1.6×10^{-3}	3.7	3.7
	Tier 2 PPE: Gloves, footwear, coveralls 20 % penetration through coated coverall 60 % dermal absorption	6.9×10^{-3}	5.5×10^{-2}	6.2×10^{-2}
Professional health care personnel Surface disinfection	**Tier 1** no PPE, 100 % penetration of clothing, 100 % dermal absorption	8.66×10^{-4}	2	2

Exposure scenario		Inhalation uptake (mg/kg b.w./day)	Dermal uptake (mg/kg b.w./day)	Total uptake (mg/kg b.w./day)
model 1/3 UserGuidance to TNsG 2002 (2004, p. 27)	**Tier 2** PPE: Gloves 50 % penetration through cotton workwear, 60 % dermal absorption	3.77×10^{-4}	6.22×10^{-2}	6.25×10^{-2}
Professional cleaning personnel Total aggregated exposure Mixing&loading + application	**Tier 1** no PPE, 100 % penetration of clothing 100 % dermal absorption	1.59×10^{-3}	3.7	3.7
	Tier 2 PPE: Gloves, footwear, coveralls 20 % penetration through coated coverall 100 % dermal absorption for mixing&loading; 60 % dermal absorption for application	6.9×10^{-3}	5.54×10^{-2}	6.23×10^{-2}
Professional health care personnel Total aggregated exposure Mixing&loading + application	**Tier 1** no PPE, 100 % penetration of clothing 100 % dermal absorption	8.66×10^{-4}	2.01	2.02
	Tier 2 PPE: Gloves, cotton workwear (50 % prentration). 100 % dermal absorption for mixing&loading; 60 % dermal absorption for application	3.77×10^{-3}	5.87×10^{-2}	6.25×10^{-2}

Exposure assessment for non-professional users

The non-professional use includes heavy-duty disinfection of objects, such as washbasin and toilet facilities. Application is by wiping with a cloth and is assumed to be performed once a week. Whilst exposure through inhalation and through the dermal route may occur during all mentioned uses, oral exposure has only to be considered during secondary exposure.

Non-professional exposure was assessed using the software ConsExpo Web tool, which is a part of TNsG 2007, and the scenario "Cleaning & washing" - "All-purpose cleaners" - "Liquid cleaner". The scenario contains exposure data for mixing & loading of a concentrate and for application of the water-diluted solution and was adopted to comply with the requirements of the BPR.

The estimated exposures are presented in table 2.3.

Table 2.3: Exposure to non-professional users

Exposure scenario	PPE	Inhalation uptake [mg/kg b.w.]	Dermal uptake [mg/kg b.w.]	Total uptake [mg/kg b.w.]
Non-professional ConsExpo -Cleaning and washing - All purpose cleaners – Liquid cleaner 100% dermal absorption for mixing&loading; 60% dermal absorption for application.	No PPE	M&L: 8.1×10^{-8} Application: 1.5×10^{-7}	M&L: 8.3×10^{-3} Application: $7.4x10^{-2}$	M&L: 8.3×10^{-3} Application: $7.4x10^{-2}$ **Total: $8.23x10^{-2}$**

Local effects

Chlorophene is classified for skin sensitisation (Skin sens. 1). The representative biocidal product is classified for skin corrosion (Skin corr. 1A) and sensitisation (Skin sens. 1), and a qualitative risk assessment was performed based on Section 4.3.2 of the ECHA guidance (ECHA, 2015). Exposure to the undiluted product will only occur during the dilution process. The potential exposure will be mainly to the hands, although accidental spills to other parts of the body, and even splashes to the eyes, cannot be ruled out. The exposure will be of short duration and will take place only one time per day. The in-use concentration of the representative biocidal product does not trigger classification for these endpoints.

The applicant has for these reasons indicated that ready-to-use formulations with chlorophene could be the relevant formulation to be marketed in the future. It was further identified that the skin corrosive property of the representative biocidal product most likely is caused by chlorocresol (CMK), another active substance present in the product, and not by chlorophene. CMK is, in contrast to chlorophene, classified as corrosive to skin and is present in the representative biocidal product in a concentration that triggers a classification for skin corrosion of the product. It might therefore be possible to reformulate the product in order to obtain a non-corrosive formulation with chlorophene. Unless the product contains other substances giving cause for concern for local effects, this concern can thus be eliminated.

Secondary exposure

Secondary exposure includes all scenarios during which exposure to the biocidal product occurs without the knowledge of the affected individual. At WGIII 2017 (Ad hoc follow up) it was decided that the EFSA guidance on dermal absorption should be applicable for the assessment of exposure to dried residues of chlorophene. Hence, a dermal absorption value of 60% was decided also for dried residues.

Depending on the location of use, secondary exposure of humans may occur by the following routes:

Table 2.4: Routes of secondary exposure

Primary use location	Secondary exposures – Examples and potential routes
Professional – public health care areas	Health care personnel (inhalation, skin contact)
Professional – public health care areas	General public (inhalation, skin contact)
Non-professionals – private homes	Residents and infants (skin contact, inhalation, ingestion)

a) Inhalation of volatilised residues indoors

As a worst case scenario for secondary exposure from inhalation, an assessment of a toddler exposed to the saturated vapour concentration of chlorophene for 24 hour was assessed, in accordance with HEEG opinion No. 13. The results are tabled below.

Table 2.5: Inhalation of volatilised residues

Inhalation of volatilised residues indoors			
	Toddler	Adult	
Body weight:	10	60	kg
SVC:	8.97E-02	8.97E-02	mg/m^3
Inhalation rate:	8	16	m^3/day
Inhalation exposure:	0.72	1.43	mg/day
Systemic exposure:	7.17E-02	2.39E-02	mg/kg b.w./day

b) Dermal exposure through skin contact

Health care personnel and the general public may be exposed to chlorophene through skin contact with treated surfaces. Secondary exposure to adults will normally occur through hand contact with treated surfaces. Secondary exposure to infants, as calculated below, represents a worst case scenario both with regard to exposed surface area and due to the contribution from oral exposure. Secondary dermal exposure to adults was therefore not assessed separately.

c) Dermal exposure through skin contact with treated surfaces – Infant

Infants may be expected to crawl on floors, touch various surfaces and to have extensive hand to mouth contact.

A scenario to assess secondary exposure to infants was chosen in accordance with the HEEG opinion 7 on choices of secondary exposure parameters for PTs 2, 3 and 4 which was agreed upon at TM I 2009 (HEEG 2009). The ConsExpo scenario *Cleaning products - Carpet Powder* –

Post Application was used with some adaptions.

A default bodyweight of 8 kg was used for the infant. A dislodgeable fraction of 55% for dried fluids from white smooth glazed tiles was used, as an approximation of tiles, porcelain, chrome and other smooth surfaces usually found in bathrooms (TNsG 2002, part 2 p. 204). Furthermore, the Cons Expo default application rate of 40 mg/m^2 was used. This application rate is related to cleaning of floors with a cleaning product. It is stated in the ConsExpo Cleaning products factsheet that the area was "quite soaked", so it is considered a rather conservative value for the use of disinfectant products.

To estimate the oral dose, in the ConsExpo “Cleaning products factsheet – Carpet powders”, it is assumed that 50% of the product that ends up on the hands is taken in orally. As the hands form about 20% of the total uncovered skin, this means that 10% of the calculated external dermal exposure is ingested via hand-mouth contact (HEEG opinion 7, 2009).

The scenario is intended to estimate secondary exposure to an infant crawling on a carpet which has been cleaned using a carpet powder and applies a contact time of one hour. Chlorophene has a very different use pattern, and will in private homes be used primarily in lavatories and bathrooms to disinfect wash basins, toilets and other objects. We have therefore found it reasonable to reduce the residence time in the bathroom to 10 minutes. Chlorophene is not intended as a general disinfectant to treat the floors in private homes, so this scenario represents a worst case situation.

The results of the exposure assessment is presented in table 2.6.

Table 2.6: Secondary exposure – Contact with treated surfaces - Infant

Intended use (PT)	Exposure scenario	PPE	Inhalation uptake [mg/kg b.w.]	Dermal uptake [mg/kg b.w.]	Oral uptake [mg/kg b.w.]	Total uptake [mg/kg b.w.]
PT 2.01 (Private area and public health disinfectants)	Cleaning and Washing – Carpet Powder – Post application (ConsExpo web)	–	1.9×10^{-7}	5.0×10^{-2}	5.7×10^{-3}	5.5×10^{-2}

2.2.1.1. Risk characterisation

Risk characterisation of production/formulation of the active substance and the biocidal product

The production/formulation process of the active substance and the biocidal product is outside the scope of the Biocidal Products Regulation. The described processes are mainly performed in closed systems resulting in minimal exposure to the operators. Exposure during production and formulation of the product was not assessed, only exposure during use of the product.

Risk characterisation for professional users

The results from the exposure calculations for professional users tabled below, shows an unacceptable risk from the use of the representative biocidal product, with the use the applied PPE agreed at the Human Health WG III 2017.

Table 2.7: Risk characterisation for professional users

Exposure Scenario		Estimated Internal Exposure [mg/kg b.w./day]	Relevant NOAEL AEL long term	Exposure /AEL
Tier 1 No PPE 100 % dermal absorption	Professional users Mixing&loading model 2 TNsG 2002	2.67 x 10^{-3}	NOAEL: 10 mg/kg b.w. /day : AEL long term: 0.035 mg/kg b.w./day	7.63x10^{-2}
Tier 2 Gloves 100 % dermal absorption	Professional users Mixing&loading model 2 TNsG 2002	2.67 x 10^{-4}	NOAEL: 10mg/kg b.w. /day : AEL long term: 0.035 mg/kg b.w./day	7.63x10^{-3}
Tier 1 no PPE, 100 % penetration of clothing; 100 % dermal absorption	Professional cleaning personnel Surface disinfection model 1/3 User Guidance to TNsG 2002 (2004, p. 27)	3.69	NOAEL: 10 mg/kg bw per day : AEL long term: 0.035 mg/kg/day	**105**
Tier 2 PPE: Gloves, footwear, coated coveralls 20 % penetration through coated coverall; 60 % dermal absorption	Professional cleaning personnel Surface disinfection model 1/3 User Guidance to TNsG 2002 (2004, p. 27)	6.2 x 10^{-2}	NOAEL: 10mg/kg bw per day : AEL long term: 0.035 mg/kg/day	**1.77**
Tier 1 no PPE, 100 % penetration of clothing; 100 % dermal absorption	Professional health care personnel Surface disinfection model 1/3 User Guidance to TNsG 2002 (2004, p. 27)	2.01	NOAEL: 10 mg/kg bw per day : AEL long term: 0.035 mg/kg/day	**57.50**
Tier 2 PPE: Gloves 50 % prentration through cotton workwear; 60 % dermal absorption	Professional health care personnel Surface disinfection model 1/3 User Guidance to TNsG 2002 (2004, p. 27)	6.22 x 10^{-2}	NOAEL: 10 mg/kg bw per day : AEL long term: 0.035 mg/kg/day	**1.78**

Exposure Scenario		Estimated Internal Exposure [mg/kg b.w./day]	Relevant NOAEL AEL long term	Exposure /AEL
Tier 1 no PPE, 100 % penetration of clothing; 100 % dermal absorption	Professional cleaning personnel Total exposure. Mixing&loading + application	3.69	NOAEL: 10 mg/kg b.w. /day : AEL long term: 0.035 mg/kg b.w./day	**106**
Tier 2 PPE: Gloves, footwear, coveralls 20 % penetration through coated coverall; 100 % dermal absorption from mixing&loading; 60 % dermal absorption from application.	Professional cleaning personnel Total exposure. Mixing&loading + application	6.23×10^{-2}	NOAEL: 10mg/kg b.w. /day : AEL long term: 0.035 mg/kg b.w./day	**1.78**
Tier 1 no PPE, 100 % penetration of clothing; 100 % dermal absorption	Professional health care personnel Total exposure. Mixing&loading + application	2.02	NOAEL: 10mg/kg b.w. /day : AEL long term: 0.035 mg/kg b.w./day	**57.6**
Tier 2 PPE: Gloves 50 % penetration through cotton workwear; 100 % dermal absorption from mixing&loading; 60 % dermal absorption from application.	Professional health care personnel Total exposure. Mixing&loading + application	6.25×10^{-2}	NOAEL: 10 mg/kg b.w. /day : AEL long term: 0.035 mg/kg b.w./day	**1.78**

Figures in bold represents exposure/AEL ≥ 1.

In conclusion unacceptable use of the representative biocidal product by professional workers is demonstrated with the use of the applied PPE agreed at the Human Health WG III 2017.

Risk characterisation for non-professional users

The results from the exposure calculations for non-professional users tabled below, shows an acceptable risk; an exposure/AEL $_{medium\ term}$ ratio of approximately 0.4. 10% of this value consists of mixing and loading, a task that may be redundant if ready-to-use products is marketed in the future.

Table 2.8: Risk characterisation for non-professional users

Exposure Scenario		Estimated Internal Exposure [mg/kg b.w./day]	Relevant NOAEL AEL medium term	Exposure /AEL
Non-professional ConsExpo - Cleaning and washing -All purpose cleaners – Liquid cleaner 100 % Dermal absorption	Mixing and loading	8.3×10^{-3}	NOAEL: 60 mg/kg b.w. /day : AEL $_{medium\ term}$: 0.21 mg/kg b.w./day	3.95×10^{-2}
Non-professional ConsExpo - Cleaning and washing - All purpose cleaners – Liquid cleaner 60 % Dermal absorption	Application	7.4×10^{-2}	NOAEL: 60 mg/kg b.w. /day : AEL $_{medium\ term}$: 0.21 mg/kg b.w./day	0.352
Non-professional Total exposure ConsExpo - Cleaning and washing - All purpose cleaners – Liquid cleaner	Total exposure (Mixing&loading + application)	8.23×10^{-2}	NOAEL: 60 mg/kg b.w. /day : AEL $_{medium\ term}$: 0.21 mg/kg b.w./day	0.392

In conclusion, safe use is demonstrated for non-professional use of the representative biocidal product in the risk assessment for systemic effects.

Risk characterisation of local effects

According to the ECHA Guidance on BPR: Vol III part B Risk Assessment, the representative biocidal product falls into the hazard category "very high" for local effects due to the classification for skin corrosion (Skin corr 1A; H314). In addition, the representative biocidal product is classified for skin sensitisation (Skin sens 1; H317), which qualifies the product for the hazard

categories "High" or "Very high" for local effects, depending on the potency.

This applies for undiluted product only, and not for the diluted in-use concentration. Exposure to the undiluted product will only occur during the dilution process. The potential exposure will be mainly to the hands, although accidental spills to other parts of the body, and even splashes to the eyes cannot be ruled out. The exposure will be of short duration and will take place only one time per day.

According to the ECHA guidance, products in this hazard category shall not normally be authorised for use by the general public due to the high risk of serious, irreversible local effects. The representative biocidal product in its current form can thus not be authorised for non-professional use. The applicant has, however, indicated during the peer review process, that ready-to-use formulations with chlorophene could be the relevant formulation to be marketed in the future. It was further identified that the skin corrosive property of the representative biocidal product most likely is caused by chlorocresol (CMK), another active substance present in the product, and not by chlorophene. CMK is, in contrast to chlorophene, classified as corrosive to skin and is present in the representative biocidal product in a concentration that triggers a classification for skin corrosion of the product. It might therefore be possible to reformulate the product in order to obtain a non-corrosive formulation. Unless the product contains other substances giving cause for concern for local effects, this concern can thus be eliminated.

For professional users, the risk from local effects can be controlled through the use of PPE. The use of chemically resistant gloves, apron and protective goggles is needed in order to ensure safe use for professional users during the dilution phase.

Risk characterisation of secondary exposure

a) Inhalation of volatilised residues indoors - Adults, children, and infants - inhalation route

As a worst-case scenario for secondary exposure from inhalation, an assessment of a toddler exposed to saturated vapour concentration of chlorophene for 24 hours was performed in accordance with HEEG Opinion No 13. The systemic exposure through inhalation of a saturated vapour concentration of chlorophene for 24 hours is thus 7.17×10^{-2} mg/kg bw/day and corresponds to an exposure/AEL $_{\text{medium term}}$ value of less than 1 and can thus be regarded as safe.

b) Dermal exposure through skin contact - Adults

Secondary exposure to infants, as calculated below, represents a worst case scenario both with regard to exposed surface area and due to the contribution from oral exposure. Secondary dermal exposure to adults was therefore not assessed separately.

c) Secondary exposure to residues on treated surfaces - Infants

A scenario to assess secondary exposure to infants was chosen in accordance with the HEEG opinion 7 on choices of secondary exposure parameters for PTs 2, 3 and 4 which was agreed upon at TM I 2009 (HEEG 2009). The ConsExpo scenario Cleaning products - Carpet Powder – Post Application, was used with some adaptions. The calculation shows that secondary exposure to an infant crawling on a treated surface, having inhalation, dermal, and the results are tabled below.

Table 2.9 Risk characterisation of secondary exposure

Exposure Scenario		Estimated Internal Exposure [mg/kg b.w/day]	Relevant NOAEL [mg/kg b.w./day] AEL medium term	Exposure /AEL
Secondary exposure. Infant crawling on a treated surface and having hand to mouth contact	Infant Cleaning and washing – Carpet Powder – Post Application (Cons Expo Web)	5.57 x 10^{-2}	NOAEL: 60 mg/kg bw per day : AEL medium term: 0.21 mg/kg/day	0.3

Figures in bold represent exposure/AEL ≥ 1.

The calculculation shows that secondary exposure to an infant crawling on a treated surface, having inhalation, dermal and oral exposure is safe, as the exposure/AEL ratio is < 1.

2.2.2. Environmental Risk Assessment

The environmental risk assessment of chlorophene has been carried out according to the principles given in the Guidance on the Biocidal Products Regulation: Volume IV Environment, Part B Risk Assessment (active substances), Version 1.0 (ECHA, 2015), hereafter referred to as the Guidance on BPR, Vol. IV Part B. For the estimation of the environmental exposure resulting from the use of the representative biocidal product, the following emission scenario documents (ESDs) have been applied: Emission Scenarios for private and public health area disinfectants and other biocidal products (RIVM, 2001), and the more recent Emission Scenario Document for Product Type 2 – Private and public health area disinfectants and other biocidal products (JRC Scientific and Technical Reports, 2011).

2.2.2.1. Fate and distribution in the environment

Based on the vapour pressure and the Henry´s Law constant, no significant volatilisation of chlorophene is to be expected. The calculated DT_{50} in the troposphere of 21.66 h indicates that no accumulation of chlorophene in the air is to be expected.

Regarding abiotic aquatic degradation, chlorophene is considered as hydrolytically stable, but photolysis is a significant degradation pathway. The photodegradation product 9H-xanthen-2-ol was formed at significant levels (max. 52.9 % of parent substance).

Regarding biodegradation, chlorophene is considered as readily biodegradable but failing the 10 day window requirement. Estimations of biodegradation of the photodegradation product 9H-xanthen-ol obtained with EPI Suite v. 4.11 (US EPA, 2012) indicate that it has a slightly faster biodegradation rate than chlorophene. Anaerobic biodegradation of chlorophene cannot be expected in sewage sludge. Chlorophene is aerobically degraded in soils. The submitted primary degradation study (DT_{50} at 12 °C = 51.6 days) has some shortcomings, and therefore the default DT_{50} value of 90 days from the Guidance on BPR, Vol. IV Part B is used for risk assessment purposes.

Distribution factors calculated by SimpleTreat v. 3.1 are 0.240 and 0.254 for sludge and water, respectively.

The K_{oc} value for chlorophene is 3398, indicating a potential for binding to soils and sediments. The log K_{ow} value for chlorophene is 4.28. The estimated log K_{ow} value (EPI Suite v. 4.11) of the photodegradation product 9H-xanthen-2-ol is 3.83. According to the Guidance on BPR, Vol. IV Part B, values greater than or equal to 3 indicate that a substance may bioaccumulate. However, the steady-state bioconcentration factors for chlorophene determined in the fish bioconcentration study are 110 L/kg and 55 L/kg (whole fish and lipid-normalised, respectively). Based on this information, chlorophene is not expected to bioaccumulate in the environment.

2.2.2.2. Effects assessment

The Predicted No-Effect Concentrations (PNECs) for chlorophene have been derived from the available effect data and based on the Guidance on BPR, Vol. IV Part B. An initial ecotoxicity estimation (EPI Suite v. 4.11) of 9H-xanthen-2-ol indicates that this photodegradation product is of less ecotoxicological concern than chlorophene. No further effects assessment of 9H-xanthen-2-ol has been performed.

Aquatic toxicity: STP, surface water and sediment

Based on Table 20 of the guidance and taking into account the only test available with aquatic micro-organisms (activated sludge, EC_{50} = 59.6 mg/L), an assessment factor of 100 can be applied. Thus, the following $PNEC_{microorganisms}$ is derived:

$PNEC_{microorganisms}$ = 596 µg/L

No valid studies on the acute effects of chlorophene on fish and aquatic invertebrates are available. However, a chronic study on both fish and daphnids are available. A 72 h growth inhibition test on algae is also available. According to the aquatic toxicity tests, the most sensitive species is *Danio rerio* (fish), with a $NOEC_{mortality}$ (30 d) of 0.58 µg/L. Since there are three NOECs from each of three trophic levels of the base-set, an assessment factor of 10 was applied to the NOEC value for fish.

$PNEC_{freshwater}$ = 0.058 µg/L

Since no experimental results are available to assess the effects of chlorophene on sediment dwelling organisms, the $PNEC_{sediment}$ was calculated according to the Equilibrium Partitioning Method from the $PNEC_{freshwater}$.

$PNEC_{sediment}$ = 4.33 µg a.i./kg suspended wet sediment

Terrestrial toxicity

Acute toxicity tests on microorganisms, earthworms and plants are available. The most acutely sensitive species is the plant *Avena sativa* with a short-term EC_{50} value of 236 mg a.i./kg dw soil (normalised to standard organic matter content). A NOEC for microorganisms (N cycle) is also available, but as this NOEC is in the same order of magnitude as the EC_{50} for *A. sativa*, it cannot be determined which is the most sensitive species and hence it cannot be used for PNEC calculation. The $PNEC_{soil}$ was therefore derived using an AF of 1000 to the EC_{50} for *A. sativa*, and a standard conversion from dry weight to wet weight soil was applied.

$PNEC_{soil}$ = 0.21 mg/kg ww soil

Fish-/invertebrate-eating birds and mammals

A short-term dietary study on mallard duck (*Anas platyrhynchos*) is available, from which an LC_{50} > 5620 mg a.i./kg feed was derived. The $PNEC_{oral}$ was calculated using this LC_{50} value and applying an assessment factor (AF_{oral}) of 3000:

$PNEC_{oral/birds}$ = 1.87 mg a.i./kg feed

A PNEC for mammals was also calculated, but as this was slightly higher than the PNEC for birds, the risk assessment for secondary poisoning has been performed for birds, and this is considered to cover the risk for secondary poisoning of mammals.

The following table summarises the PNEC values which are used in this risk assessment.

Table 2.10: PNEC values for chlorophene

Compartment	PNEC
STP (microorganisms)	0.60 mg/L
Freshwater	5.8E-05 mg/L = 0.058 µg/L
Sediment	4.3E-03 mg/kg susp wet sediment
Soil	0.21 mg/kg wet soil
Biota (top predator)	1.87 mg/kg feed

2.2.2.3. PBT and POP assessment

PBT assessment

Chlorophene fulfills the T criterion based on the lowest aquatic NOEC of 0.58 µg/L.

The experimentally derived log K_{ow} value for chlorophene is 4.28. According to the Guidance on BPR, Vol. IV Part B, a log K_{ow} ≥ 3 indicates that the substance may bioaccumulate. However, the steady-state bioconcentration factors determined in the fish bioconcentration study are 110 L/kg and 55 L/kg (whole fish and lipid-normalised, respectively). Based on this information, the B criterion is not fulfilled and chlorophene is not expected to bioaccumulate in the environment.

Regarding persistency, in the first ready biodegradation test (CO_2 evolution) > 60 % degradation was observed, but not within the 10 day window. In the second ready biodegradation test (manometric respirometry) 9 % degradation was observed. In this test the initial a.s. concentrations were high and not considered environmentally relevant. According to the inherent biodegradation test, chlorophene is inherently biodegradable. Anaerobic biodegradation cannot be expected, but in soils, chlorophene is aerobically degraded. An indicative primary degradation DT_{50} of 51.6 days (12 °C) has been derived. It is considered unlikely that the actual DT_{50} should be higher than the default DT_{50} value of 90 days from the Guidance on BPR, Vol. IV Part B, which is used for risk assessment purposes. The trigger for the P criterion under the REACH legislation is a DT_{50} of 120 days. Chlorophene is not considered to fulfil the P/vP-criterion.

In conclusion, chlorophene fulfills the T criterion but is not considered to fulfill the P or B criteria. Based on the available information, chlorophene should therefore not be considered a PBT/vPvB substance.

The substance 9H-xanthen-2-ol was formed in significant amounts (max 52.9 % of parent substance) in the photodegradation study. Estimations of the environmental fate and ecotoxicity

obtained with EPI Suite v. 4.11 (US EPA, 2012) indicate that this photodegradation product biodegrades slightly faster than chlorophene. The log K_{ow} is estimated to be lower than that of chlorophene and based on QSAR it is estimated to be similarly or less ecotoxic than chlorophene. However, as the T criterion is fulfilled for chlorophene, it cannot be excluded that 9H-xanthen-2-ol would also fulfil the T criterion. Based on this screening, 9H-xanthen-2-ol is not considered to fulfil the P or B criteria.

POP assessment

The vapour pressure of chlorophene is < 1.0E-03 Pa at 25 °C and the calculated DT_{50} in the troposphere is 21.7 h. This clearly indicates that no accumulation of chlorophene in the air is to be expected, and that the criteria for long-range transport potential (vapour pressure < 1000 Pa and half-life in air > 2 days) are not fulfilled. Chlorophene is relatively strongly adsorbed to soil and sediment (K_{oc} = 3398), thus the mobility is relatively low.

The experimentally derived steady-state BCF_{fish} is approximately 100 L/kg for whole fish and the lipid-normalised BCF_{fish} is approximately 55 L/kg. The bioaccumulation criterion of 5000 L/kg is hence not fulfilled.

In conclusion, chlorophene is not considered to fulfil the POP criteria.

2.2.2.4. Exposure assessment

The emissions of chlorophene as used in the representative biocidal product have been assessed by means of the Guidance on BPR, Vol. IV Part B and the ESDs for PT 2 (2001 and 2011). The only direct emissions of chlorophene to the environment when used as disinfectant are via wastewater. Sewage water treatment plants (STPs) can thus be regarded as the only directly exposed compartment. Surface water and sediments could however be indirectly exposed via STP effluents, and soil and groundwater could be indirectly exposed via STP sludge application. The exposure to all these compartments has therefore been assessed. The photodegradation product 9H-xanthen-2-ol has not been considered in the exposure assessment. The estimations of environmental fate and ecotoxicity (EPI Suite v. 4.11; US EPA, 2012) indicate that this breakdown product is of less environmental concern than chlorophene.

Chlorophene is intended to be used for heavy-duty disinfection in hospitals by professional cleaners or professional health care personnel. It is also meant for small-scale private domestic use.

The exposure assessment follows a two-tiered approach. The standard consumption-based emission scenarios for hospitals and domestic use from the ESDs for PT 2 are applied in tier 1. These scenarios allow the calculation of the daily emission rates ($Elocal_{water}$) based on the amount of litres of water used per day. For tier 1, the default amount of water containing active substance discharged to the STP per day has been taken into account. Originally, the applicant submitted a proposed tier 2 assessment which involved a reduction of the amount of water (10 % of the amount of water used in tier 1, both for professional and non-professional use), in order to more appropriately reflect the intended small scale use. However, the WG (WG III 2017) concluded that a refinement of the PT 2 exposure scenarios is only applicable to ready-to-use (RTU) products, and in that case, the RTU scenario for small scale applications as described in the Technical Agreements for Biocides (ECHA, 2017) should be applied. This RTU scenario is based on the scenario for institutional use given in Table 2 of the ESD from 2011, but the treated surface area is reduced to 25 m^2.

Hence, a tier 2 exposure assessment for the use in hospitals/institutional areas (professional use) by professionals has been carried out according to the RTU scenario, which is applicable only for RTU biocidal products containing chlorophene.

The RTU scenario is not developed with regards to domestic (non-professional) use. Hence, no scenario which represents the non-professional use of chlorophene in an RTU product exists. As an attempt to nevertheless reflect the small scale use, it was agreed by the WG (WG III 2017) that the use on lavatories only (as described in the ESD from 2011, Table 4) could be calculated as a tier 2 approach. It is emphasised that this exposure estimation does not reflect the use in RTU products.

According to the applicant, the use in hospitals is considered to be the main source of emissions to the environment. It is assumed that although not reflected in the emission calculations (due to no suitable RTU scenario for non-professional use), the release from private use will be considerably lower than the release from hospitals.

Predicted Environmental Concentrations (PECs) were calculated from the daily emission rates according to the Guidance on BPR, Vol. IV Part B. The resulting PECs are summarised in the following table.

Table 2.11: PEC values for chlorophene in the relevant environmental compartments

	Professional use		Non-professional use	
	Tier 1	Tier 2[1]	Tier 1	Tier 2[2]
PEC_{STP} [mg/L]	4.3E-03	1.1E-04	4.0E-03	1.1E-03
$PEC_{surface\ water}$ [mg/L]	4.3E-04	1.1E-05	4.0E-04	1.1E-04
$PEC_{sediment}$ [mg/kg wwt]	0.03	8.5E-04	0.03	8.5E-03
PEC_{soil} [mg/kg wwt]	0.01	3.8E-04	0.01	3.8E-03
$PEC_{groundwater}$ [mg/L]	2.4E-04	6.4E-06	2.2E-04	6.4E-05
$PECoral_{predator,\ fish}$ [mg/kg]	0.02	6.3E-04	0.02	6.3E-03
$PECoral_{predator,\ earthworm}$ [mg/kg]	0.34	9.0E-03	0.31	0.09

[1] RTU scenario for institutional areas
[2] Small scale use (lavatory) only – not an RTU-specific scenario

Note on groundwater

The PEC value for groundwater/porewater in tier 1 is slightly above the groundwater threshold concentration of 0.1 µg/L (1.0E-04 mg/L). However, in tier 2 the PEC is below this threshold. Thus, the risk of leaching to groundwater is low for chlorophene when used for small scale disinfection. Groundwater concentrations have furthermore been calculated using the FOCUS PEARL v.4.4.4 model. All nine groundwater scenarios as described in the report from the Groundwater Scenarios Workgroup (FOCUS, 2000) were run. The results indicate that no or negligible amounts of chlorophene (< < 0.1 µg/L) leach to groundwater in all the nine scenarios.

Note on aggregated exposure

Chlorophene is also intended used as an active substance in PT 3, for the disinfection of poultry barns. This use has been evaluated separately. The use pattern differs significantly between PT 2 and PT 3. Regarding STPs, which would be the most relevant compartment to consider in an

aggregated exposure assessment, the outcome of the current assessment of chlorophene in PT 3 results in a condition that chlorophene should not be released directly from the poultry barn into public STPs. STPs and hence surface waters and sediments are therefore not likely exposed to chlorophene from both PT 2 and PT 3 use. Nevertheless, for national authorisations it should be considered whether exposure from other sources have a significant influence on the risk assessment.

2.2.2.5. Risk characterisation

The PEC/PNEC ratios calculated for chlorophene used as an active substance in the representative biocidal product in PT 2 are summarised in the following table.

Table 2.12: PEC/PNEC ratios from the use of chlorophene in a PT 2 disinfectant

Compartment	Professional use		Non-professional use	
	Tier 1	Tier 2[1]	Tier 1	Tier 2[2]
STP	7.2E-03	1.9E-04	6.7E-03	1.9E-03
Surface water	**7.39**	0.20	**6.89**	**1.97**
Sediment	**7.39**	0.20	**6.89**	**1.97**
Soil	0.07	1.8E-03	0.06	0.02
Biota, aquatic: secondary poisoning	0.01	3.4E-04	0.01	3.4E-03
Biota, terrestrial: secondary poisoning	0.18	9.0E-03	0.17	0.05

[1] RTU scenario for institutional areas
[2] Small scale use (lavatory) only – not an RTU-specific scenario

Unacceptable risks are identified when the PEC/PNEC ratios exceeds 1. The use of the representative biocidal product as a general PT 2 disinfectant according to the standard scenarios given in the ESDs for PT 2, i.e. tier 1, would result in risks to the aquatic environment (surface water and sediment). This applies to both professional and non-professional use (separately as well as combined). The use of chlorophene as an active substance in a general disinfectant product should therefore not be regarded as acceptable, neither for professional use nor non-professional use, based on these calculations.

However, the tier 2 assessment for professional use, which represents the use in RTU products, is expected to be acceptable for the environment based on the current assessment.

The tier 2 assessment of the non-professional use has not been shown acceptable following this assessment, since there are risks to the aquatic environment (surface water and sediment). It should however be noted that even though the tier 2 assessment for non-professional use reflects a smaller scale use than as a general disinfectant, it does not reflect a use in RTU products specifically.

Of the emission scenarios evaluated in this assessment, the small-scale use in RTU products is the only safe scenario.

2.2.3. Assessment of endocrine disruptor properties

The endocrine disruptor properties have not been assessed as defined in Regulation (EU) No 2017/2100 and it is therefore not possible to finally conclude on the exclusion criteria related to Article 5(1)(d) and 10(1)(a), and on whether chlorophene shall be considered a candidate for

substitution related to Article 10(1)(e) . This is in line with paragraph 16 of the "Implementation of scientific criteria to determine the endocrine-disrupting properties of active substances currently under assessment"[3].

2.2.3.1. Summary of the contributions to the public consultation for potential candidates for substitution and alternative substances or technologies

Chlorophene met the interim criteria for endocrine-disrupting properties according to Article 5(3) of the BPR as it is classified as a carcinogen category 2 and toxic for reproduction category 2. Consequently, the information on the fulfilment of the conditions for considering the active substance as a candidate for substitution was made publicly available at https://echa.europa.eu/potentialcandidates-for-substitution-previous-consultations on 10 February 2017, in accordance with the requirements of Article 10(3) of Regulation (EU) No 528/2012.

A public consultation was carried out to determine if any chemical or non-chemical alternatives were available for the intended use of chlorophene. Interested third parties were invited to submit relevant information by 10 April 2017.

A summary of the responses received is available Appendix IV.

2.3. Overall conclusions

The outcome of the assessment for chlorophene in product-type 2 is specified in the BPC opinion following discussions at the 34th meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

2.4. List of endpoints

The most important endpoints, as identified during the evaluation process are listed in Appendix I.

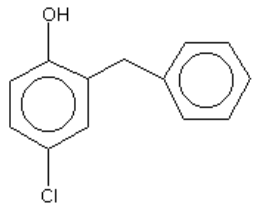
[3] See document: Implementation of scientific criteria to determine the endocrine –disrupting properties of active substances currently under assessment (https://circabc.europa.eu/sd/a/48320db7-fc33-4a91-beec-3d93044190cc/CA-March18-Doc.7.3a-final-%20EDs-%20active%20substances%20under%20assessment.docx).

Appendix I: List of endpoints

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Name)	Chlorophene
Product-type	PT 2

Identity

Chemical name (IUPAC)	2-Benzyl-4-chlorophenol
Chemical name (CA)	Phenol, 4-chloro-2-(phenylmethyl)-
CAS No	120-32-1
EC No	204-385-8
Other substance No.	Not applicable
Minimum purity of the active substance as manufactured (g/kg or g/l)	966 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	No relevant impurities present
Molecular formula	C13H11ClO
Molecular mass	218.7 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	45.9 °C (purity 97.9 %)
Boiling point (state purity)	Decomposes before boiling
Thermal stability / Temperature of decomposition	Decomposes at 110 °C (purity 97.9 %)
Appearance (state purity)	White to slight yellow solid (purity 98 %)
Relative density (state purity)	1.317 at 20 °C (purity 97.9%)
Surface tension (state temperature and concentration of the test solution)	57.3 mN/m at 20 °C (conc. 0.09 g/L 77 % saturation, purity 97.9 %) Chlorophene is surface active
Vapour pressure (in Pa, state temperature)	< 1.0E-03 Pa at 20 °C and 25 °C 1.66E-02 Pa at 50 °C (purity 97.7 %)
Henry's law constant (Pa m^3 mol^{-1})	1.87 × 10^{-03} Pa·m^3/mol at 20 °C
Solubility in water (g/l or mg/l, state temperature)	pH 5 at 10 °C: 0.083 g/L

	pH 7 at 20 ºC: 0.117 g/L pH 7 at 30 ºC: 0.199 g/L (Purity 97.9 %) Temperature dependence on water solubility was observed. An effect of pH-value is not expected.
Solubility in organic solvents (in g/l or mg/l, state temperature)	The solubility of chlorophene in methanol and toluene at 10, 20 and 30 °C is > 250 g/L (purity 97.9 %)
Stability in organic solvents used in biocidal products including relevant breakdown products	The active substance as manufactured does not include an organic solvent. Therefore no study regarding its stability in organic solvents was performed.
Partition coefficient (log P_{OW}) (state temperature)	pH 4 at 25ºC: 4.276 pH 7 at 25ºC: 4.275 pH 9 at 25ºC: 4.175 pH dependence on log Pow was not observed. An effect of temperature is not expected. (purity 96.8 %)
Dissociation constant	pKa = 9.59 (purity 96.8 %)
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Abs maxima at 284 nm (ε = 3995 $L \cdot mol^{-1} \cdot cm^{-1}$) No absorption above 290 nm. (purity 97.7 %)
Flammability or flash point	Not flammable
Explosive properties	Not explosive
Oxidising properties	Not an oxidiser
Auto-ignition or relative self ignition temperature	Does not undergo spontaneous combustion.

Classification and proposed labelling[4]

with regard to physical hazards	None

[4] Harmonised classification [10th ATP to CLP (Commission Regulation (EU) 2017/776)].

with regard to human health hazards	Carc. 2, H351 Suspected of causing cancer Repr. 2, H361f Suspected of damaging fertility Acute Tox. 4, H332 Harmful if inhaled Skin Irrit. 2, H315 Causes skin irritation Skin Sens. 1 H317 May cause an allergic skin reaction Eye Dam. 1, H318 Causes serious eye damage STOT RE 2, H373 May cause damage to kidneys through prolonged exposure Pictograms: GHS05, GHS07, GHS08 Signal Word Code: Danger
with regard to environmental hazards	Aquatic Acute 1, H400 Very toxic to aquatic life M-factor = 1 Aquatic Chronic 1, H410 Very toxic to aquatic life with long lasting effects M-factor = 100 Pictograms: GHS09 Signal Word Code: Danger

Chapter 2:Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method) Impurities in technical active substance (principle of method)	Chlorophene and its impurities were dissolved in acetonitrile and analysed by reverse phase HPLC-DAD (Purospher STAR 100 RP-18, DAD: 286 nm for pure active and 200 nm for impurities). External standards used. MS-ESI was used for detection of minor impurities, no calibration standards was used.

Analytical methods for residues

Soil (principle of method and LOQ)	Soil samples were extracted with acetonitrile and filtered (PTFE, 0.45µm). The extracts were analysed with HPLC-MS (Column: Prodigy 5u ODS3. Detection: ES-MS). Parent ion was detected (217 amu). External standard used for quantification. The LOQ for chlorophene in soil was set to 0.01 mg/kg

Air (principle of method and LOQ)	Air was aspirated through a Tenax adsorption tube for 6 hours. The Tenax tube was extracted with acetonitrile. The extract was analysed with reverse phase HPLC-MS (Column: Purospher STAR 100RP-18e. Detection: ESI-MS). Parent ion was detected (217 amu). External standard used for quantification. The LOQ for chlorophene in air was set to 0.3 µg/m^3 air.
Water (principle of method and LOQ)	Samples with <10 µg/L were extracted with SPE (Chromabond C18-200 mg/3 mL). Samples ≥10 µg/L were used as is. Samples were analysed with reverse phase HPLC-MS/MS (Column: Sciex RP18. Detection: Turbo Ion spray-MS, Additional UV detection (205 nm) was used). Parent ion (217 amu) detected. External standard used for quantification. The LOQ for chlorophene in water was set to 0.1 µg/L.
Body fluids and tissues (principle of method and LOQ)	Not applicable since chlorophene is not classified as toxic or highly toxic.
Food/feed of **plant** origin (principle of method and LOQ for methods for monitoring purposes)	Not submitted
Food/feed of **animal** origin (principle of method and LOQ for methods for monitoring purposes)	Not submitted

Chapter 3: Impact on Human Health

Absorption, distribution, metaboljorism and excretion in mammals

Rate and extent of oral absorption:	70 % is assumed.
Rate and extent of dermal absorption[5]:	60 % for the dilutions of 0.09 % and 0.5 % 100 % for corrosive formulations.
Distribution:	The highest concentration of chlorophene radioactivity was found in the kidney during the whole measuring period and this affinity of renal tissue is likely to play a role in the suggested nephrotoxicity of this compound.
Potential for accumulation:	No evidence of accumulation.

[5] The dermal absorption value is applicable for the active substance and might not be usable in product authorization.

Rate and extent of excretion:	Most of the administered chlorophene was excreted and the tissue levels were generally low within 3d post administration (except for the dermal study where 32 % of the total dose was found at the skin site).The studies indicated that enterohepatic circulation was involved in chlorophene disposition.
Toxicologically significant metabolite(s)	The major *in vivo* metabolites detected after chlorophene exposure were glucuronyl conjugates of chlorophene and hydroxy-chlorophene in faeces and urine.

Acute toxicity

Rat LD_{50} oral	3852 mg/kg bw
Rat LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	2.43 mg/L/4h (Acute Tox. 4, H332 Harmful if inhaled)

Skin corrosion / irritation	Skin Irrit. 2 (H315 Causes skin irritation)
Eye irritation	Eye dam. 1 (H318: Causes serious eye damage)
Respiratory tract irritation	No classification for STOT SE is warranted
Skin sensitisation (test method used and result)	3 positive Buehler tests provide collectively a sufficient basis for classifying chlorophene as a skin sensitiser even though they have some shortcomings. Human data from clinical tests also support this conclusion. Skin Sens. 1 (H317: May cause an allergic skin reaction)
Respiratory sensitisation (test method used and result)	No data

Repeated dose toxicity

Short term

Species / target / critical effect	Rat oral gavage / kidney / absolute and relative kidney weight significant increased. Mild to moderate nephrophaty with an increased incidence and severity with increased dose. Rabbit dermal systemic / kidney / lesions involving histopathological changes. Rabbit dermal local / skin lesions explained by the irritant properties of the active.
Relevant oral NOAEL / LOAEL	$NOAEL_{rat}$ = 62.5 mg/kg bw/day (16 days) $LOAEL_{rat}$ = 125 mg/kg bw/day (16 days)
Relevant dermal NOAEL / LOAEL	Overall $NOAEL_{rabbit\ systemic}$ = 25 mg/kg bw/day (3-4 weeks) Overall $LOAEL_{rabbit\ systemic}$ = 100 mg/kg bw/day (3-4 weeks) $NOAEL_{rabbit\ local}$ = 1 mg/kg bw/day (4 weeks) $LOAEL_{rabbit\ local}$ = 5 mg/kg bw/day (4 weeks)
Relevant inhalation NOAEL / LOAEL	No data

Subchronic

Species/ target / critical effect	Rat oral gavage / kidney / increased absolute and relative kidney weights and microscopic kidney lesions.
Relevant oral NOAEL / LOAEL	<u>90 day rat:</u> NOAEL of 60 mg/kg bw/day (extrapolated from LOAEL of 120)
Relevant dermal NOAEL / LOAEL	No data
Relevant inhalation NOAEL / LOAEL	No data

Long term

Species/ target / critical effect	Rat oral gavage / kidney / nephropaty
Relevant oral NOAEL / LOAEL	$NOAEL_{rat}$ = 10 mg/kg bw/day (extrapolated from LOAEL, 2 year) $LOAEL_{rat}$ = 30 mg/kg bw/day (lowest dose tested, 2 year)
Relevant dermal NOAEL / LOAEL	No data
Relevant inhalation NOAEL / LOAEL	No data

Genotoxicity	No classification justified

Carcinogenicity

Species/type of tumour	Female rat / two rare transitional cell carcinomas. Male mice / renal neoplasm. (Cars. 2; H351 Suspected of causing cancer)
Relevant NOAEL/LOAEL	Please refer long-term studies.

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	Rat / reduced bodyweight gain and food intake Rabbit/ death and reduced bodyweight
Relevant maternal NOAEL	NOAEL = 100 mg/kg bw/day
Relevant developmental NOAEL	NOAEL = 100 mg/kg bw/day (highest dose tested)

Fertility

Species/critical effect	Rat / reduced female fertility index (Repr Cat 2; H361f Suspected of damaging fertility)
Relevant parental NOAEL	Not applicable, effect seen in lowest dose tested in males (LOAEL = 60 mg/kg bw/day)
Relevant offspring NOAEL	NOAEL = 60 mg/kg /bw/day
Relevant fertility NOAEL	NOAEL = 60 mg/kg /bw/day

Neurotoxicity

Species/ target/critical effect	No data

Developmental Neurotoxicity

Species/ target/critical effect	

Immunotoxicity

Species/ target/critical effect	No data

Developmental Immunotoxicity

Species/ target/critical effect	

Other toxicological studies

Supplementary study on the induction of drug-metabolising enzymes.

Medical data

A single report of contact dermatitis is reported in the literature.

Summary

	Value	Study	Safety factor
$AEL_{long-term}$	0.035 mg/kg bw/day (1)	Two year study in rat	100 (inter- and intraspecies factors 10) and 3 (extrapolating from LOAEL to NOAEL) for the rat study and 2 (lacking information on the second species)
$AEL_{medium-term}$	0.21 mg/kg bw/day (1)	95 day rat study	100 (inter- and intraspecies factors 10) and 2 (lacking information on the second species)
$AEL_{short-term}$	0.7 mg/kg bw/day (1)	Developmental studies in rat and rabbits	100 (inter- and intraspecies factors 10)
ARfD	Not established	Not established	Not established
ADI	0.05 mg/kg bw/day	Two year study in rat	100 (inter- and intraspecies factors 10) and 3 (extrapolating from LOAEL to NOAEL) for the rat study and 2 (lacking

		information on the second species)

[1] *Corrected for oral absorption (70 %)*

MRLs

Relevant commodities	Not relevant

Reference value for groundwater

According to BPR Annex VI, point 68	Not available

Dermal absorption

Study (*in vitro/vivo*), species tested	*In vivo* dermal absorption study in rats.
Formulation (formulation type and including concentration(s) tested, vehicle)	A commercial disinfectant solution containing 5 % chlorophene. The tested concentrations were 0.05 %, 0.5 % and 5 % (formulation diluted in water).
Dermal absorption values used in risk assessment	60 % for the dilutions of 0.09 % and 0.5 %, as well as for dried residues. 100 % for corrosive formulations. For product authorisation, the applicability of the test available must be decided.

Acceptable exposure scenarios (including method of calculation)

Formulation of biocidal product	Not applicable
Intended uses	Heavy-duty disinfection of surfaces.
Industrial users	Not applicable
Professional users	Heavy-duty disinfection of surfaces and objects by professional cleaning personnel and professional heath care workers in hospitals. Scenarios used: Mixing&loading model 2 and *Professional Operator diluting and mixing disinfectant and wiping surfaces using a wrung cloth (User guidance to TNsG 2002 (2004); TNsG 2007)* No acceptable use identified with the PPE agreed at HH WG 2017 (except exposure during the mixing and loading phase).

Non-professional users	Heavy-duty disinfection of objects such as washbasins, toilet facilities. Scenario used: *"Cleaning & washing" - "All-purpose cleaners" - "Liquid cleaner"* (ConsExpo web). A risk was identified in the local risk assessment as non-professional users cannot use the representative product safely. For non-professional users, an acceptable risk was identified in the systemic risk assessment.
General public	Secondary exposure through inhalation and dermal contact with treated surfaces. Scenarios used: Assessment of inhalation of a saturated vapour concentration of chlorophene. Secondary exposure to an infant having inhalation, dermal and oral contact: "*Cleaning products - Carpet Powder – Post Application" (*ConsExpo web*)* No risks for secondary exposure were identified.
Exposure via residue in food	Not relevant

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	pH 4: stable at 50 °C pH 7: DT_{50} = 44.4 d at 50 °C pH 9: DT_{50} = 37.4 d at 50 °C
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	DT_{50} = 0.7 h. at pH 7 and 20-30 °C Relevant degradation product: 9H-xanthen-2-ol (max. 52.9 % of parent)
Readily biodegradable (yes/no)	Readily biodegradable, but failing the 10 day window requirement
Inherent biodegradable (yes/no)	yes

Biodegradation in freshwater	Experimental DT_{50} not available. Other relevant information: – Article on biodegradation of chlorophene in river water: 60 % CO_2 evolution after 4 weeks. – Based on the degradation behaviour of other comparable aromatic phenolic compounds, biodegradation of chlorophene under natural conditions is expected Default DT_{50} = 50 d (readily biodegradable, failing 10 day window requirement) used in the risk assessment.
Biodegradation in seawater	Not available
Non-extractable residues	Not quantified. Other relevant information: – Results from the inherent biodegradation study indicate strong, non-extractable binding to the inoculum. – Results from the adsorption/desorption studies indicate that the non-extractable residues would consist mainly of primary degradation products, not chlorophene.
Distribution in water / sediment systems (active substance)	Not available. Other relevant information: Based on other available degradation studies and the degradation behaviour of other comparable aromatic phenolic compounds, rapid dissipation of chlorophene from the water is expected. It is furthermore expected that a relatively high amount of non-extractable residues in sediment is formed, but that this mainly would consist of degradation products rather than parent substance.
Distribution in water / sediment systems (metabolites)	Not available

Route and rate of degradation in soil

Mineralization (aerobic)	Not available
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (20°C, aerobic): Primary dissipation DT_{50} = 21.4 d at 23 °C Normalised to 51.6 d at 12 °C Default DT_{50} = 90 d (for substances which are readily biodegradable but failing the 10 day window requirement) used in the risk assessment.
degradation in the saturated zone:	Not available
Field studies (state location, range or median with number of measurements)	Not available

Anaerobic degradation	Anaerobic biodegradation of chlorophene cannot be expected in sewage sludge. Low degree of anaerobic degradation in pork liquid manure, to levels of approx. 70 % after 64 days.
Soil photolysis	Not available
Non-extractable residues	Not available
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Not available
Soil accumulation and plateau concentration	Not available

Adsorption / desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	<u>Adsorption kinetics test</u> (four soil types, nominal chlorophene conc. 8 mg/L) K_d = 16-98 mL/g K_{oc} = 1361-2974 mL/g <u>Desorption kinetics test</u> (four soil types, nominal chlorophene conc. 8 mg/L) K_d = 19-115 mL/g K_{oc} = 1635-3470 mL/g <u>Freundlich adsorption isotherm test</u> (four soil types, nominal chlorophene conc. 5-50 mg/L) K_d = 25-156 mL/g K_{oc} = 2210-4726 mL/g Mean Koc of 3398 from Freundlich adsorption isotherm test used in the risk assessment.

Fate and behaviour in air

Direct photolysis in air	Not available
Quantum yield of direct photolysis	Not available
Photo-oxidative degradation in air	Model calculation (AOPWIN v. 1.91): DT_{50} = 21.7 h 24 h average OH radical concentration: $0.5 \cdot 10^6$ / cm^3
Volatilization	Based on the Henry's Law constant (calculated, $3.7 \cdot 10^{-3}$ Pa · m^3/mol), no significant volatilisation of chlorophene from water is to be expected. Slow evaporation from inert surface: 40 % of originally applied chlorophene present after 125 d.

Reference value for groundwater

According to BPR Annex VI, point 68	Not available

Monitoring data, if available

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study)	<u>STPs, Missouri and Ohio USA</u> Average conc. in influent and effluent water: 14.8 µg/L and 0.8 µg/L, respectively Average conc. in STP sludge over 3 days: 23.0 mg/L <u>STPs, Germany (49 sites)</u> Median conc. in effluent water: 0.05 µg/L (min: < LOD of 0.01 µg/L, max: 0.70 µg/L) <u>STP, Germany (1 site)</u> Average conc. in influent and effluent water over 6 days: 0.30 ± 0.11 µg/L and 0.11 ± 0.02 µg/L, respectively <u>Bays, rivers and lakes, USA (18 sites)</u> Conc. between < 0.11 µg/L and 0.21 µg/L <u>Streams and rivers, Germany (16 sites)</u> Median conc.: 0.01 µg/L (min: < LOD of 0.005 µg/L, max: 0.10 µg/L) <u>Estuary, San Francisco USA</u> Not found in surface water, only in STP effluent at max 12 ng/L **Biota:** <u>Fish (muscle tissue of breams), German rivers (2 sites)</u> Measurement of conc. in fish muscle tissue over several years: 1994: 2.9 ng/g ww 1996: 3.3 ng/g ww 2003: < LOQ of 0.25 ng/g ww
Ground water (indicate location and type of study)	Not available
Air (indicate location and type of study)	Not available

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity
Fish			
Zebrafish (*Danio rerio*)	30 d post hatch (OECD 210)	Mortality Hatching Growth	$NOEC_{mortality}$ = 5.8E-04 mg/L $NOEC_{hatching}$ = 0.07 mg/L $NOEC_{growth}$ = 0.02 mg/L (mean measured concentrations)
Invertebrates			
Daphnia magna	21 d (EEC 20 / OECD 2011)	Reproduction Mortality	$NOEC_{reproduction}$ = 6.7E-03 mg/L $NOEC_{mortality}$ = 0.03 mg/L (mean measured concentrations)
Algae			
Pseudokirchneriella subcapitata	72 h (OECD 201)	Growth inhibition	E_rC_{50} = 0.177 mg/L NOEC = 0.093 mg/L (geometric mean measured concentrations)
Microorganisms			
Activated sludge	3 h (ISO 8192 / OECD 209)	Respiration inhibition	EC_{50} = 59.6 mg/L (nominal concentrations)

Effects on earthworms or other soil non-target organisms

Acute toxicity to earthworms (*Eisenia fetida*)	OECD 207: 14 d LC_{50} = 428 mg/kg dw (nominal concentrations)
Acute toxicity to terrestrial plants (*Brassica napus*, *Glycine max*, *Avena sativa*)	OECD 208: 14 d EC_{50} *B. napus* = 462 mg/kg dw 14 d EC_{50} *G. max* = 1073 mg/kg dw 14 d EC_{50} *A. sativa* = 236 mg/kg dw (nominal concentrations, normalised to standard organic matter content)
Reproductive toxicity to.....	Not available

Effects on soil micro-organisms

Nitrogen mineralization	OECD 216: 29 d NOEC, inhibition = 816 mg/kg dw 29 d NOEC, stimulation = 81.6 mg/kg dw (nominal concentrations, normalised to standard organic matter content)
Carbon mineralization	OECD 217:

	29 d EC_{50} > 19 mg/kg dw 29 d LOEC > 19 mg/kg dw (nominal concentrations)

Effects on terrestrial vertebrates

Acute toxicity to mammals	See Chapter 3: Impact on Human Health
Acute toxicity to birds (*Colinus virginianus*)	US-EPA FIFRA: 14 d LD_{50} > 2510 mg/kg bw 14 d NOEC = 631 mg/kg bw (nominal concentrations)
Dietary toxicity to birds (*Anas platyrhynchos*)	US-EPA FIFRA / ASTM E857-81: 5 d + 3 d LC_{50} > 5620 mg/kg feed (nominal concentrations)
Reproductive toxicity to birds	Not available

Effects on honeybees

Acute oral toxicity	Not available
Acute contact toxicity	Not available

Effects on other beneficial arthropods

Acute oral toxicity	Not available
Acute contact toxicity	Not available
Acute toxicity to ……..	Not available

Bioconcentration

Bioconcentration factor (BCF)	OECD 305: Steady-state BCF = 107-110 (whole fish), 55-56 (lipid-normalised)
Depuration time (DT_{50})	< 24 h (24 h after initiation of the depuration phase, no chlorophene was detected in any of the fish samples)
Depuration time (DT_{90})	< 24 h (24 h after initiation of the depuration phase, no chlorophene was detected in any of the fish samples)
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable

Chapter 6: Other End Points

Appendix II: List of Intended Uses

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m² min max	g a.s./m² min max	
Professional and private heavy-duty disinfection	[redacted]	**Bacteria:** *Bacillus subtilis; Pseudomonas aeruginosa; Alcaligenes faecalis; Corynebacterium sp.* **Mould fungi:** *Penicillium brevicaule; Chaetomium globosum; Aspergillus niger; Trichoderma viridae; Aureobasidium pullulans, Alternaria alternate; Cladosporium cladosporioides; Rhodotorula rubra; Fusarium solani; Geotrichum candidum*	EC (Emulsifiable concentrate)	5%, in-use conc. is 0.09%	Wiping/ mopping	1	Daily (professional) Weekly (non-professional)	0.9 g/L	0.04 L/m² (ConsExpo –Cleaning products fact sheet. Worst case value for application)	0.036 g/m² (ConsExpo –Cleaning products fact sheet. Worst case value for application)	Please note that the representative biocidal product is an example product, not intended to be placed on the EU market. The product contains 3 other active substances which have not been assessed.

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
A2.6(01)	Stroech, K.	1992	Preventol BP (2-Benzyl-4-chlorophenol) Synthesis. Date: March 1992 CONFIDENTIAL Bayer AG, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS
A2.7(01) A2.8(01)	Erstling, K.	2007	Determination of the main and minor components in Preventol BP, 5-Batch analysis. Date: 2007-07-24 CONFIDENTIAL Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2005/0148/11 GLP Unpublished	Yes	LANXESS
A3.1(01) A3.10(01) A3.13(01)	Jungheim, R.	2007	Physicochemical properties of chlorophene. Date: 2007-07-24 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2006/0173/02 GLP Unpublished	Yes	LANXESS
A3.2(01)	Olf, G.	2006	Vapor pressure, physical-chemical properties. Date: 2006-01-24 Bayer AG, Leverkusen, Germany Report No. 05/018/01 GLP Unpublished	Yes	LANXESS
A3.2(02)	Beiell, U.	2007	Calculation of Henry's Law	Yes	LANXESS

[6] ***Section Number/Reference Number*** should refer to the section number in Doc III-A or III-B. If the study is non-key, and hence not summarised in Doc III but mentioned in Doc II, it should be included in the reference list alongside related references and its location in Doc II indicated in brackets. (If there is a need to include a cross-reference to PPP references then an additional column can be inserted).

[7] ***Author's Name*** should include the author's surname before initial (s) to enable the column to be sorted alphabetically. If the Human Rights Charter prevents author's surnames on unpublished references being included in non-confidential documents, then it will be necessary to consider including 'Unpublished [number/year & letter] ' in Doc II, and both ' Unpublished [number/year & letter]' and the 'Authors Name' in the reference list'. This may necessitate the need for an additional column to state whether a reference is unpublished which can then be sorted.

[8] ***Title, Source (where different from company), Company, Report No., GLP (where relevant), (Un)Published*** should contain information relevant to each item (ideally on separate lines within the table cell for clarity). If useful, the name of the electronic file containing the specific study/reference could be added in brackets.

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Constant of Chlorophen (2-benzyl-4-chlorophenol). Date: 2007-07-26 Dr. Knoell Consult GmbH, Leverkusen, Germany Report No. 2007/07/26/UB Non-GLP Unpublished		
A3.3(01)	Kraus, H.	2006	2-Benzyl-4-chlorophenol / Appearance. Date: 2006-06-04 LANXESS Deutschland GmbH, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS
A3.4(01)	Jungheim, R.	2007	Spectraldata of chlorophene. Date: 2007-07-20 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2006/0173/03 GLP Unpublished	Yes	LANXESS
A3.5(01)	Jungheim, R.	2006	Determination of the water solubility (flask method) of chlorophene at 10 °C, 20 °C and 30 °C. Date: 2006-08-15 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2005/0148/07 GLP Unpublished	Yes	LANXESS
A3.5(02) A3.9(03)	Erstling, K.	2002	Water solubility, Preventol O extra in Schuppen. Date: 2002-02-15 Bayer AG, Leverkusen, Germany Report No. A00/0068/02 LEV GLP Unpublished	Yes	LANXESS
A3.6(01) A3.9(01)	Greenwood, J.	2003	BCP: Determination of the partition coefficient. Date: 2003-06-04 Covance Laboratories Ltd, England Report No. 2126/3-D2149 GLP Unpublished	Yes	Clariant
A3.7(01)	Jungheim, R.	2007	Solubility of chlorophene in methanol and toluene at 10 °C, 20 °C and 30 °C.	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Date: 2007-07-16 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2006/0173/04 GLP Unpublished		
A3.9(02)	Feldhues, E	2006	Statement Partition coefficient n-octanol/water of Preventol O extra, Temperature and pH dependence. Date: 2006-11-20 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Non-GLP	Yes	LANXESS
A3.9(04)	Jungheim, R.	2004	Solubility of Preventol O extra in organic solvents. Date: 2004-07-26 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. A02/0162/04 LEV GLP Unpublished	Yes	LANXESS
A3.11(01)	Heinz, U.	2007	Determination of safety-relevant data of Preventol BP. Date: 2007-06-18 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Study No. 2007/00653 GLP Unpublished	Yes	LANXESS
A3.17(01) A8.1(02)	Kraus, H.	2006	2-Benzyl-4-chlorophenol (chlorophene) / reactivity towards container material. Date: 2006-06-01 LANXESS Deutschland GmbH, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS
A3.17(02)	Kraus, H.	2008	2-Benzyl-4-chlorophenol (chlorophene) / reactivity towards container material. Date: 2008-01-07 LANXESS Deutschland GmbH, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS
A4.1(01)	Erstling, K.	2007	Validation of a HPLC method for the determination of the relevant main and minor components in	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Preventol BP. Date: 2007-07-24 CONFIDENTIAL Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2005/0148/10 GLP Unpublished		
A4.2a	Meinerling, M. and Herrmann, S.	2008	Validation of an analytical method for the determination of Preventol BP (chlorophene) in soil. Date: 2008-01-15 IBACON GmbH, Rossdorf, Germany Report No. 33345101 GLP Unpublished	Yes	LANXESS
A4.2b	Königer, A.	2009	Validation of an analytical method for the determination of Preventol BP in air samples. Date: 2009-11-02 Currenta GmbH & Co. OHG, Leverkusen, Germany Report No. 2005/0148/14 GLP Unpublished	Yes	LANXESS
A4.2c	Meinerling, M.	2007	Validation of an analytical method for the determination of Preventol BP (chlorophene) in water. IBACON GmbH, Rossdorf, Germany Project No. 33346101 GLP Unpublished	Yes	LANXESS
A5.3.1(01)	Kugler, M.	2003	Determination of the antimicrobial effects of Preventol BP against bacteria and fungi. Date: 2003-04-16 Bayer AG, Leverkusen, Germany Report No. 2003-04-14 Non-GLP Unpublished	Yes	LANXESS
A5.3.1(02)	Bomblies, L. and Wedde, A	2000	Preventol BP (active substance). Determination of the “Minimal Inhibitory Concentration (MIC) against various test microorganisms. Date: 2000-09-16 Labor L+S, Bad-Bocklet-Großenbrach, Germany Report No. 01020940 Non-GLP	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Unpublished		
A5.3.1(03)	Gerharz, T.	2010	Determination of disinfectant properties of Preventol® BP in accordance to EN 1276 (bactericidal effect) and EN 1650 (fungicidal effect). Date: 2010-07-06 LANXESS Deutschland GmbH, Leverkusen, Germany Unpublished	Yes	LANXESS
A5.3.1(04)	Gerharz, T. and Rech, M.	2014	Determination of the mycobactericidal efficacy of 2-Benzyl-4-chlorophenol in accordance with DIN EN 14204_2012 (clean conditions). Date: 2014-07-11 LANXESS Deutschland GmbH, Leverkusen, Germany Unpublished	Yes	LANXESS
A5.3.1(05)	Gerharz, T. and Rech, M.	2014	Determination of the mycobactericidal efficacy of 2-Benzyl-4-chlorophenol in accordance with DIN EN 14348:2005 (clean conditions). Date: 2014-07-11 LANXESS Deutschland GmbH, Leverkusen, Germany Unpublished	Yes	LANXESS
A6.1.1	[redacted]	1983	Ortho-Benzyl Parachlorophenol, (Chlorophen): Acute Oral Toxicity in the Rat. [redacted] Non-GLP Unpublished	Yes	Clariant
A6.1.2	[redacted]	1983	Ortho-Benzyl Parachlorophenol, (Chlorophen): Acute Percutaneous Toxicity in the Rat. [redacted] Non-GLP Unpublished	Yes	Clariant
A6.1.3	[redacted]	1983	Ortho-Benzyl Parachlorophenol, (Chlorophen): Acute Inhalation Toxicity in the Rat. [redacted] Non-GLP Unpublished	Yes	Clariant, LANXESS
A6.1.4	[redacted]	2000	Primary Dermal Irritation Study in Rabbits with Preventol BP (EPA/OECD/MAFF Guidelines).	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			[redacted] GLP Unpublished		
[Doc II-A, section A6.1.4] Non-key	[redacted]	1983	Acute Dermal Irritation/Corrosion Test in Rabbits. [redacted] Non-GLP Unpublished	Yes	Clariant LANXESS
[Doc II-A, section A6.1.4] Non-key	[redacted]	1983	Preventol BP - Examination of its Irritative Effects on Skin and Mucosa. [redacted] Non-GLP Unpublished	Yes	LANXESS
A6.1.4	[redacted]	1983	Ortho-Benzyl Parachlorophenol, (Chlorophen): Acute Eye Irritation/Corrosion Test in Rabbits. [redacted] Non-GLP Unpublished	Yes	Clariant
A6.1.5	[redacted]	2001	Dermal Sensitization Study in Guinea Pigs – Closed Patch Test Technique with Preventol BP [redacted] GLP Unpublished	Yes	LANXESS
[Doc II-A, section A6.1.5] Non-key	[redacted]	2002	Preventol BP Schuppen – Study for the skin sentitization effect in guinea pigs (Buehler Patch Test). [redacted] GLP Unpublished	Yes	LANXESS
[Doc II-A, section A6.1.5] Non-key	[redacted]	1986	Preventol BP - Test for sensitizing effect on guinea pig skin ("Open Epicutaneous Test" according to Klecak). [redacted] GLP Unpublished	Yes	LANXESS
[Doc II-A, section A6.1.5]	[redacted]	2005	Chlorophen: Dermal sensitization study in Guinea pigs – closed patch technique. [redacted] GLP	Yes	LANXESS, AH Marks Study submitted by LANXESS in the CLH process
[Doc II-A, section	Kahn *et al*	1970	Depigmentation caused by phenolic detergent germicides.		Submitted by

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
A6.1.5]			Arch Dermatol 192, 177-187. Published		LANXESS in the CLH process
[Doc II-A, section A6.1.5]	Dohn	1980	Dermatological patients not employed in handicraft or factories. Contact Dermatitis 6, 148-150. Published		Submitted by LANXESS in the CLH process
A6.2(01)	Kao, L.R. and Birnbaum, L.S.	1986	Disposition of o-Benzyl-p-Chlorophenol in Male Rats. Systemic Toxicology Branch, NIEHS, Research Triangle Park, NC, USA Report No. *Journal of Toxicology and Environmental Health*, 18, p. 441 -458, 1986 Non-GLP Published	No	--
A6.2(02)	[redacted]	1994	Dermal Absorption of 14C-o-Benzyl-p-Chlorophenol From a 5% Formulation. [redacted] GLP Unpublished	Yes	LANXESS
A6.3.1(01)	Sendelbach, L.E.	1982	Repeated Oral Dose Study of o-Benzyl-p-Chlorophenol in F344/N Rats. Battelle, Columbus, OH, USA. Report No. NTP Technical Report TR424. Non-GLP Published	No	NTP
[Doc II-A, section A6.3.1] Non-key	Sendelbach, L.E.	1982	Repeated Oral Dose Study of o-Benzyl-p-Chlorophenol in B6C3F1 Mice. Battelle, Columbus, OH, USA. Report No. Technical Report TR424. Non-GLP Published	No	NTP
[Doc II-A, section A6.3.2] Non-key	[redacted]	1984	Ortho-Benzyl Parachlorophenol (Chlorophen): Preliminary Dermal Toxicity Study in the Rabbit. [redacted] GLP Unpublished	Yes	Clariant, LANXESS
[Doc II-A, section A6.3.2]	[redacted]	1989	Ortho-Benzyl Parachlorophenol (Chlorophen): 21-Day Percutaneous Toxicity Study in the	Yes	Clariant, LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
Non-key			Rabbit. [redacted] GLP Unpublished		
A6.3.2(01)	[redacted]	1985	Ortho-Benzyl Parachlorophenol, (Chlorophen): 21-Day Dermal Toxicity Study in the Rabbit. [redacted] GLP Unpublished	Yes	Clariant, LANXESS
A6.3.2(02)	[redacted]	1985	Preventol BP - Subacute toxicological study in rabbits (3-week trial with cutaneous application). [redacted] GLP Unpublished	Yes	LANXESS
A6.4.1(01)	National Toxicology Program (NTP) and Birnbaum *et al*., 1986	1994	NTP Technical Report on the Toxicology and Carcinogenesis Studies of o-Benzyl-p-Chlorophenol (CAS No. 120-32-1) in F344/N Rats and B6C3F1 Mice. National Toxicology Program, Research Triangle Park, NC, USA. Report No. NTP Technical Report TR 424 GLP Published	No	NTP
[Doc II-A, section A6.5] Non-key	[redacted]	2005	2-Benzyl-4-chlorphenol (Preventol BP) – Exploratory Subchronic Toxicity Study in Male Rats (16-Weeks Administration via Diet). [redacted] Non-GLP Unpublished	Yes	LANXESS
A6.5(01) also filed: A6.7(01)	Hejtmancik, M. et al.	1988	The Chronic Gavage Study of o-Benzyl-p-Chlorophenol (CAS No. 120-32-1) in Fischer 344 Rats. Battelle, Columbus, OH, USA. Report No. National Toxicology Program Technical Report TR424. GLP Published	No	NTP
A.6.6(1)	Mortelmans, K. *et al*.	1986	Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. EG&G Mason Research Institute & SRI International.	No	NTP

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Report No. Environ. Mutagen. 8, (Suppl. 7), 1-119 Non-GLP Published		
A6.6.2(01)	[redacted]	1994	Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. [redacted] GLP Unpublished	Yes	Clariant, LANXESS
A6.6.3(01)	[redacted]	2005	BCP: Mutation at the hprt locus of L5178Y Mouse Lymphoma Cells using the Microtitre® Fluctuation Technique. [redacted] GLP Unpublished	Yes	Clariant
A6.6.3(02)	Caspary	1988	The mutagenic activity of selected compounds at the TK locus: rodent vs. human cells. Report No. Mutation Research 196, p.61-81 Non-GLP Published	No	--
A6.6.4(01)	[redacted]	1990	Nipacide BCP: Assessment of Clastogenc Action on Bone Marrow Erythrocytes in the Micronucleus Test. [redacted] GLP Unpublished	Yes	Clariant, LANXESS
[Doc II-A, section A6.6.4] Non-key	[redacted]	1972	Mutagenic Study with Santophen I in Albino Mice. [redacted] Non-GLP Unpublished	No	LANXESS
A6.6.5	[redacted]	2009	Chlorophene: Single Cell Gel Electrophoresis (Comet) Assay in the Male Mouse: *In Vivo*. [redacted] GLP Unpublished	Yes	LANXESS
A6.7(01) also filed: A6.5(01)	Hejtmancik, M. *et al.*	1988	The Chronic Gavage Study of o-Benzyl-p-Chlorophenol (CAS No. 120-32-1) in Fischer 344 Rats. Battelle, Columbus, OH, USA. Report no. National Toxicology Program Technical Report TR424. GLP	No	NTP

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Published		
A6.7(02)	Hejtmancik, M. *et al.*	1988	The Chronic Gavage Study of o-Benzyl-p-Chlorophenol (CAS No. 120-32-1) in B6C3F1 mice. Battelle, Columbus, OH, USA. Report no. National Toxicology Program Technical Report TR424. GLP Published	No	NTP
A6.7(03)	National Toxicology Program	1995	One-year initiation/promotion study of o-Benzyl-p-Chlorophenol (CAS No. 120-32-1) in Swiss (CD-1®) Mice (Mouse Skin Study). National Toxicology Program Technical Report TR424 Published	No	NTP
A6.8.1(01)	[redacted]	1985	Chlorophen: Teratology Study in the Rat. [redacted] GLP Unpublished	Yes	Clariant, LANXESS
A6.8.1(02)	[redacted]	1985	Chlorophen: Effects of Oral Administration upon Pregnancy in the Rabbit. [redacted] GLP Unpublished	Yes	Clariant, LANXESS
A6.8.1(3)	[redacted]	1984	Teratogenicity test in the rat Embryotoxicity (Including Teratogenicity) Study with Preventol BP Technical in the Rat. [redacted] GLP Unpublished	Yes	LANXESS
[Doc II-A, section A6.8.1(4)] Non-key	[redacted]	1985	Chlorophen: Effects of Oral Administration upon Pregnancy in the Rat. 1. Dosage Range-Finding Study. [redacted] Non-GLP Unpublished	Yes	Clariant, LANXESS
[Doc II-A, section A6.8.1(4)] Non-key	[redacted]	1985	Chlorophen: Effects of Oral Administration upon Pregnancy in the Rabbit. 1. Dosage Range-Finding Study. [redacted] Unpublished	Yes	Clariant, LANXESS
[Doc II-A,	[redacted]	1979	A Segment II Teratology Study	No	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
section A6.8.1(5)] Non-key			with Santophen I in Rabbits. [redacted] Non-GLP Unpublished		
A6.8.2(01)	[redacted]	1973	Reproduction Study with Santophen I in Albino Rats. [redacted] Non-GLP Unpublished	No	LANXESS
A6.8.2(02)	[redacted]	1973	Perinatal and Lactation Study with Santophen I in Albino Rats. [redacted] Non-GLP Unpublished	No	LANXESS
A6.8.2(3)	[redacted]	2008	Two Generation Reproduction Toxicity Study by Gavage in Wistar Rats. [redacted] GLP Unpublished	Yes	Clariant, LANXESS
[Doc II-A, section A6.8.]	Mylchreest E and Harris SB	2013	Reproductive and developmental studies in laboratory animals. Methods Mol Biol. 2013; 947:275-94. Published	-	--
A6.10	Kao *et al*	1986	Effect of o-Benzyl-p-Chlorophenol on Drug-Metabolizing Enyzmes in Rats. Systemic Toxicology Branch, NIEHS, Research Triangle Park, NC, USA. Biochemical Pharmacology, 35(4), p. 613-620, 1986. Non-GLP Published	No	--
A6.12.1	[redacted]	2007	Medical statement – 2-benzyl-4-chlorophenol (BP). [redacted] Unpublished	Yes	LANXESS
A6.12.6	Sonnex & Rycroft	1986	Allergic Contact Dermatitis from Orthobenzyl P Chlorophenol in a Drinking Glass Cleaner. St, John's Hospital for Diseases of the Skin, London, England. Contact Dermatitis; 14 (4). 247-248. Published	No	Study submitted by LANXESS in the CLH process
A6.12.6	Rothe *et al*	1993	Contact dermatitis caused by	No	Study

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			formaldehyde-free disinfectants. Hygiene Medizin 18, 167-175		submitted by LANXESS in the CLH process
A7.1.1.1.1 (01)	Greenwood, J.	2003	BCP: Evaluation of hydrolysis as a function of pH (HPLC screen). Date: 2003-06-04 Covance Laboratories Ltd, North Yorkshire, England Report No. 2126/4-D2149 GLP Unpublished	Yes	Clariant
A7.1.1.1.2 (01)	Meinerling, M. and Herrmann, S.	2007	Phototransformation of Preventol BP (Chlorophene) in Water. Date: 2007-06-08. IBACON GmbH, Rossdorf, Germany Project No. 33341176 GLP Unpublished	Yes	LANXESS
A7.1.1.1.2 (01)	Freudenberger, Ch. and Wesener, J.R.	2011	Structure elucidation of the major photolysis product of Preventol BP (chlorophene) Date: 2011-02-25 Currenta GmbH & Co. OHG, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS
A7.1.1.1.2 (01)	Meinerling, M.	2011	Non-GLP Statement on IBACON Project 33341176, Photolytic degradation of Preventol BP IBACON GmbH, Rossdorf, Germany Non-GLP Unpublished	Yes	LANXESS
A7.3.1(01)	Fàbregas, E.	2006	Calculation of indirect photodegradation of chlorophen. Date: 2006-06-06 Dr. Knoell Consult GmbH Report No. KC-PD-03/06 Non-GLP Unpublished	Yes	LANXESS
A7.3.2	Nitsche, M.	2011	Vaporisation behaviour of Preventol BP (Chlorophen) from an inert surface (glass petri dish). Date: 2010-09-22 LANXESS Deutschland GmbH, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
A7.1.1.2.1 (01)	Bealing, D.J. and Watson, S.	2002	BCP: Assessment of ready biodegradability by measurement of carbon dioxide evolution. Date: 2002-02-26 Covance Laboratories Ltd, Harrogate, England Report No. 2126/5 GLP Unpublished	Yes	Clariant
A7.1.1.2.1 (02) Non-key	Reis, K.H.	2007	Ready biodegradability of chlorophene in a manometric respiratory test. Date: 2007-02-19 IBACON GmbH, Rossdorf, Germany Project No. 31115163 GLP Unpublished	Yes	LANXESS
A7.1.1.2.2 (01)	Reis, K.H.	2007	Inherent Biodegradability of Chlorophene in a Zahn-Wellens/EMPA Test. Date: 2007-05-15 IBACON GmbH, Rossdorf, Germany Project No. 31111165 GLP Unpublished	Yes	LANXESS
A7.1.1.2.1 (03) Non-key	Swisher, R.D. and Gledhill	1973	Microbial degradation of O-Benzyl-p-Chloro-phenol CSMA, in: Proceedings of the 60th Annual Meeting, Published by Chemical Specialities Manufacturers Association Inc. Non-GLP Published	No	-
A7.2.1 Non-key	Nitsche, M	2011	Biodegradation of Preventol BP (Chlorophen) in soil under aerobic conditions. Date: 2011-09-14 LANXESS Deutschland GmbH, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS
A7.1.2.1.2 (01)	Reis, K.H.	2007	Anaerobic biodegradability of Chlorophene in digested sludge: Measurement of gas production. Date: 22-03-2007 IBACON GmbH, Rossdorf, Germany Project No. 31113168 GLP Unpublished	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
[Doc II-A, section 4.1.1.2] Non-key	Gerharz, T.	2011	Biodegradation of 5 mg/kg Preventol BP (2-benzyl-4-chlorophenol) in pork liquid manure under anaerobic conditions Date: 2011-06-20 LANXESS Deutschland GmbH, Leverkusen, Germany Report No. D 2011-10.3 Non-GLP Unpublished	Yes	LANXESS
A7.1.2.2.2 (justification for non-submission of data) Part of CAR for CMK as Doc III-A7.1.2.2.2 (01)	Möndel, M.	2009	^{14}C-Preventol CMK: Aerobic degradation of ^{14}C-Preventol CMK in two different aquatic sediment systems. Date: 2009-03-26 RLP AgroScience GmbH, Neustadt, Germany Study No. AS85 GLP Unpublished	Yes	LANXESS
A7.1.2.2.2 (justification for non-submission of data) Part of CAR for CMK as Doc III-A7.1.2.2.2 (02)	Möndel, M.	2010	^{14}C-Preventol CMK: Characterisation of non-identified radioactivity of ^{14}C-Preventol CMK in an aquatic sediment system. Date: 2010-05-21. RLP AgroScience GmbH, Neustadt, Germany Study No. AS139 GLP Unpublished	Yes	LANXESS
A7.2.2 (justification for non-submission of data) Part of CAR for OPP as Doc III-A7.2.1	Fliege, R	2005	(phenyl-UL-^{14}C)ortho-phenylphenol: Aerobic Soil Metabolism in one European Soil Date: 2005-03-23 Bayer CropScience AG, Monheim, Germany Report No. MEF-05/072 GLP Unpublished	Yes	LANXESS
[Doc II-A, section 4.1.1.2] Non-key	Loehr, R.C., Matthews, J.E.	1992	Loss of organic chemicals in soil: Pure compound treatability studies University of Texas, Austin, USA *Journ. Soil Contam.,* 1(4):339-360 Non-GLP Published	No	-
[Doc II-A, section	Sattar, M.A.	1989	Fate of chlorinated cresols from environmental samples	No	-

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
4.1.1.2] Non-key			Bangladesh Agricultural University, Bangladesh *Chemosphere,* 19(8/9):1421-1426 Non-GLP Published		
[Doc II-A, section 4.1.1.2] Non-key	Haider, K., Jagnow, G., Kohnen, R., Lim, S.U	1974	Abbau chlorierter Benzole, Phenole und Cyclohexan-Derivate durch Benzol und Phenol verwertenden Bodenbakterien unter aeroben Bedingungen. *Arch. Microbiol.* 96:183-200 Non-GLP Published	No	-
[Doc II-A, section 4.1.1.2] Non-key	Weijnen, P.H.C., van den Berg, R., van den Berg, S.	1989	Biodegradatie van chloorfenolen in de bodem. RIVM, Bilthoven, The Netherlands Report No. 728603005 Non-GLP Published	No	-
A7.1.3(01)	Jungheim, R.	2006	Determination of the Adsorption Coefficient (K_{oc}) by High Performance Liquid Chromatography (HPLC) Method of Chlorophene. Date: 2006-08-15 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2005/0148/05 GLP Unpublished	Yes	LANXESS
A7.2.3.1(01)	Meinerling, M.	2007	Determination of the Adsorption / Desorption Behaviour of 2-Benzyl-4-chlorophenol (Preventol BP). Date: 2007-06-15 IBACON GmbH, Rossdorf, Germany Project No. 31112195 GLP Unpublished	Yes	LANXESS
A7.1.2.1.1 (01)	Werner, F.A., Taulli, T.A., Michael, P.R. and Williams, M.A.	1983	Estimation and verification of the environmental fate of *o*-benzyl-*p*-chlorophenol Monsanto Company, Missouri, USA and Analytical Biochemistry Laboratories, Missouri, USA *Arch. Environ. Contam. Toxicol.* 12, 569-575 Non-GLP Published	No	LANXESS
A7.1.2.1.1	Ternes,	1988	Simultaneous Determination of	No	-

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
(02)	T.A., Stumpf, M., Schuppert, B., Haberer, K.		Antiseptics and Acidic Drugs in Sewage and River Water ESWE-Institute for Water Research and Water Technology, Wiesbaden, Germany *Vom Wasser* 90:295-309 Non-GLP Published		
A7.4.2 A7.5.5 Non-key	Fàbregas, E.	2007	Calculation of the Bioconcentration Factor (BCF) of Chlorophene. Date: 2007-05-09 Dr. Knoell Consult GmbH, Mannheim, Germany Report No. KC-BCF-03/07 Non-GLP Unpublished	Yes	LANXESS
A7.4.3.3.1	[redacted]	2009	Bioconcentration: Flow-through Fish Test with Chlorophene (Preventol BP). [redacted] GLP Unpublished	Yes	LANXESS
A7.4.1.1(01) Non-key	[redacted]	1986	Preventol BP (2-benzyl-4-chlorophenol): Fish toxicity, Brachydanio rerio. [redacted] Non-GLP Unpublished	Yes	LANXESS
A7.4.1.2(01) Non-key	Caspers, N.	1986	Preventol BP (2-benzyl-4-chlorophenol): Toxicity, Daphnia magna Date: September 1986 Bayer AG, Leverkusen, Germany Non-GLP Unpublished	Yes	LANXESS
A7.4.1.3(01)	Egeler, Ph., Junker, Th. and Seck, C.	2006	Preventol BP technical: A study on the toxicity to algae (Pseudokirchneriella subcapitata). Date: 2006-02-28 ECT Oekotoxikologie GmbH, Flörsheim am Main, Germany Report No. AN1AO GLP Unpublished	Yes	LANXESS
A7.4.1.3(0	Caspers, N.	1986	Preventol BP (2-benzyl-4-	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
2) Non-key			chlorophenol): Growth inhibition test Algae. Date: August 1986 Bayer AG, Leverkusen, Germany Non-GLP Unpublished		
A7.4.1.4	Caspers, N. & Müller, G.	1991	Untersuchungen zur Bakterientoxizität von Preventol BP Schuppen Date: 1991-02-25 Bayer AG, Leverkusen, Germany Report No. 221 A/91 B GLP Unpublished	Yes	LANXESS
A7.4.3.2(01) Non-key	[redacted]	2007	Toxicity of 2-Benzyl-4-chlorophenol (Preventol BP) to Zebra-Fish (Danio rerio) in an Early-Life Stage Test. [redacted] GLP Unpublished	Yes	LANXESS
A7.4.3.2(02)	[redacted]	2008	Toxicity of 2-Benzyl-4-chlorophenol (Preventol BP) to Zebra-Fish (Danio rerio) in an Early-Life Stage Test. [redacted] GLP Unpublished	Yes	LANXESS
[Doc II-A, section 4.2.1.4] Non-key	Roex, E.	2002	Sensitivity of the zebrafish (*Danio rerio*) early life stage test for compounds with different modes of action *Env. Poll.* 120:355-362 Non-GLP Published	No	-
A7.4.3.4	Weyers, A.	2007	Daphnia magna Reproduction Test. Date: 2007-02-12 Bayer Industry Services GmbH & Co., Leverkusen, Germany Project No. 2006/0173/01 GLP Unpublished	Yes	LANXESS
A7.5.1.1(01) Non-key	Reis, K.H.	2007	Effects of Chlorophene on the activity of the soil microflora in the laboratory.	Yes	LANXESS

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Date: 2007-03-16 IBACON GmbH, Rossdorf, Germany Report No. 31116080 GLP Unpublished		
A7.5.1.1(02)	Schulz, L.	2012	Preventol BP – Effects on the activity of soil microflora (Nitrogen transformation test). Date: 2012-05-07 BioChem Agrar, Labor für biologische und chemische Analytik, Gerichshain, Germany Non-GLP Unpublished	Yes	LANXESS
A7.5.1.2	Lührs, U.	2007	Acute Toxicity (14 Days) of Chlorophene to the Earthworm *Eisenia fetida* in Artificial Soil with 5% Peat. Date: 2007-01-17 IBACON GmbH, Rossdorf, Germany Project No. 31117021 GLP Unpublished	Yes	LANXESS
A7.5.1.3	Bützler, R. and Meinerling, M	2007	Effects of Chlorophene on Terestrial (Non-Target) Plants: Seedling Emergence and Seedling Growth Test. Date:2007-03-08 IBACON GmbH, Rossdorf, Germany Project No. 31118084 GLP Unpublished	Yes	LANXESS
A7.5.3.1.1 (01) Non-key	[redacted]	1983	An Acute Oral Toxicity Study in the Bobwhite with NIPACIDE BCP. [redacted] Non-GLP Unpublished	Yes	LANXESS, Clariant
A7.5.3.1.2 (02)	[redacted]	1984	A Dietary LC50 Study in the Mallard with NIPACIDE BCP. [redacted] Non-GLP Unpublished	Yes	LANXESS, Clariant
B2.3(01)	Jiritschka,	2007	Formulation type and appearance	Yes	Bayer

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
B3.1(01)	W.		of the product. Date: 2007-06-26 Bayer HealthCare AG, Monheim, Germany Non-GLP Unpublished		HealthCare AG
B3.2(01) B3.3(01)	Jiritschka, W.	2007	Declaration on explosive and exidising properties. Date: 2007-06-25 Bayer HealthCare AG, Monheim, Germany Non-GLP Unpublished	Yes	Bayer HealthCare AG
B3.4(01) B3.10(01)	Heinz, U.	2007	Determination of safety-relevant data of [redacted] (Preventol TP LXS 80051) Date: 2007-12-11 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2007/01385 GLP Unpublished	Yes	Bayer HealthCare AG
B3.5(01) B3.6(01) B3.8(01) B3.10(02)	Erstling, K.	2007	Physical chemical properties of [redacted] (Preventol TP LXS 80051) Date: 2007-10-09 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2007/0095/01 GLP Unpublished	Yes	Bayer HealthCare AG
B3.7	Erstling, K.	2008	Accelerated Storage Test of [redacted] (Preventol TP LXS 80051) Currenta GmbH & Co. OHG, Leverkusen, Germany Report No. 2007/0095/04 GLP Unpublished	Yes	Bayer HealthCare AG
B3.7(01)	Jiritschka, W.	2007	[redacted], declaration on GLP studies. Date: 2007-07-17 Bayer HealthCare AG, Leverkusen, Germany Non-GLP Unpublished	Yes	Bayer HealthCare AG
B3.7(02)	Erstling, K.	2007	Low temperature storage test of [redacted] (Preventol TP LXS 80051) Date: 2007-10-09 Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany	Yes	Bayer HealthCare AG

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			Report No. 2007/0095/05 GLP Unpublished		
B3.7(03)	Jungheim, R.	2011	Long term storage test (3 years) at ambient temperature of [redacted] (Preventol TP LXS 80051). Currenta GmbH & Co. OHG, Leverkusen, Germany Report No. 2007/0095/06 GLP Unpublished	Yes	Bayer Animal Health GmbH
B4.1(01)	Erstling, K.	2007	Validation of an analytical method for the determination of the main components in [redacted] (preventol TP LXS 80051) Date: 2007-12-10 CONFIDENTIAL Bayer Industry Services GmbH & Co. OHG, Leverkusen, Germany Report No. 2007/095/03 GLP Unpublished	Yes	Bayer HealthCare AG
B5.10	Gerharz, T.	2010	Determination of disinfectant properties of Preventol® TP LXS 80051 ([redacted]) in accordance to EN 1276 (bactericidal effect) and EN 1650 (fungicidal effect). Date: 2010-07-15 LANXESS Deutschland GmbH, Leverkusen, Germany Unpublished	Yes	LANXESS
B6.1.1	[redacted]	2006	Preventol TP LXS 80051– Acute toxicity in the rat after oral administration. [redacted] GLP Unpublished	Yes	Bayer HealthCare AG
B6.1.2	[redacted]	2006	Preventol TP LXS 80051– Acute toxicity in the rat after dermal administration. [redacted] GLP Unpublished	Yes	Bayer HealthCare AG
B6.2	[redacted]	2006	Preventol TP LXS 80051– Evaluation of corrosive properties	Yes	Bayer HealthCare

Section No / Reference No[6]	Author(s)[7]	Year	Title[8] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
			by using an artificial 3D-Skin model. [redacted] GLP Unpublished		AG
B6.3	[redacted].	2007	Preventol TP LXS 80051– Study for the Skin Sensitization Effect in Guinea Pigs (Guinea Pig Maximization Test according to Magnusson and Kligman). [redacted] GLP Unpublished	Yes	Bayer HealthCare AG
B6.4	[redacted]	1994	Dermal Absorption of 14C-o-Benzyl-p-Chlorophenol from a 5% Formulation. [redacted] GLP Unpublished	Yes	Bayer AG

20 April 2017

Appendix IV: Summary of the public consultation of chlorophene PT 2 and 3

Chlorophene met the interim criteria for endocrine-disrupting properties according to Article 5(3) of the BPR as it is classified as a carcinogen category 2 and toxic for reproduction category 2. Consequently, the information on the fulfilment of the conditions for considering the active substance as a candidate for substitution was made publicly available at https://echa.europa.eu/potentialcandidates-for-substitution-previous-consultations on 10 February 2017, in accordance with the requirements of Article 10(3) of Regulation (EU) No 528/2012. Interested third parties were invited to submit relevant information on alternative substances and technologies in the period 10 February 2017 to 10 April 2017.

Substances details

Substance name	Chlorophene
Product type(s)	2, 3
Intended use(s)	The active substance is used as a heavy-duty disinfectant for both professional and limited private use in PT 2 and to control pathogenic micro-organisms in industrial poultry barns and similar facilities by professional workers in PT3.
EC number	204-385-8
CAS number	120-32-1
eCA	Norway
Which conditions of Article 10(1) are met	Chlorophene fulfilled the interim criteria as an active substance with endocrine disrupting properties due to the classification as Carc. 2 and Repr. 2. (according to Article 5(3) of the BPR). Hence, it fulfilled the exclusion criteria given in article 5 (1)(d) of the BPR and therefore the condition of Article 10(1)(a).

Summary

A public consultation regarding chlorophene PT 2 and 3 took place from 10/02/2017 to 10/04/2017.

The applicant has argued that chlorophene has an essential use and is an important disinfection management tool for disease prevention, and that only a limited number of other active substances could cover similar use conditions as chlorophene. They have compiled a comparison with other evaluated substances and concluded that not all intended uses have identified alternatives that could be used.

Three Member States and Norway responded to the public consultation regarding possible use of chlorophene in PT2 and alternatives. None of the responses indicated any essentiality of the use of chlorophene for general disinfection or against any specific organism as the substance seems not to be on the market in several MS and Norway, or is only used in cleaning products. Alternative substances or methods seem to exist to prevent the effect of the indicated target

organisms, e.g. Escherichia coli, Pseudomonas aeruginosa, Aspergillus species and Mycobacteria in these countries.

As the number of respondents in the consultation is small, an in-depth evaluation of alternative substances and methods is not possible, and no clear conclusion can be drawn on the need of chlorophene for use in PT2. However, there is no clear indication of the essentiality of the substance.

The table below, provided by ECHA, presents the confidential and non-confidential documents that were received.

Documents received

Title File name	Relevant for product-type	Description	Submitter
Public consultation on Chlorophene_PT2.docx [pc_chlorophene_non_conf_comment_01]	2	Report from different organisations in Estonia indicating that there are no products containing chlorophene in product type 2 on Estonian market.	Member State - Estonia
Public consultation on Chlorophene_PT3.docx [pc_chlorophene_non_conf_comment_02]	3	Report from different organisations in Estonia indicating that there are no products containing chlorophene in product type 3 on Estonian market.	Member State - Estonia
Chlorophene_PublicConsultationMar2017.docx [pc_chlorophene_non_conf_comment_03]	2, 3	Two products containing several ingredients including chlorophene exist in the Finnish Chemicals Product Register (http://www.ketu.fi), one for cleaning medical instruments by dentists and the second to prevent build-up of calcium on pipes and scaling in toilets. It is not clear if the products are biocides at all. Control of Mycobacteria tuberculosis or Mycobacterium bovis is not a claimed use of these products. Last outbreak of bovine tuberculosis took place in 1982 in Finland. It is a dangerous animal disease that has to be reported to animal health authorities. According to animal health ETT there are several alternative active substances which can be used to control bovine tuberculosis, for example chlorine, iodine, sodium hypochlorite, formaldehyde, glutaraldehyde, hydrogen peroxide, peracetic acid.	Member State - Finland
SNGTV consultation ECHA chlorophène 2017 04 06.pdf [pc_chlorophene_non_conf_comment_04]	3	Document by the French Society of veterinary techniques (in French) describing the use of chlorophene for different animal species. According to SNGTV, the lack of this product would require additional chemical input to treat the target organisms simultaneously, at least for the cunicole (rabbit) species. The document concludes that the importance of the CMR risk of the active substance prevails over the socioeconomic concern driven by the potential withdrawal of chlorophene from the market.	SNGTV National NGO - France

Chlorophene_Public commenting.7z [pc_chlorophene_non_conf_comment_05]	2, 3	Position paper The applicant provides a justification for the approval of the active substance, considering that: - chlorophene fulfils the interim ED criteria which are planned to be replaced in a timeframe overlapping with the decision on the substance. - the interim ED criteria are scientifically unjustified for the identification of an ED substance. - chlorophene has an essential use and is an important disinfection management told for disease prevention. The application identified only a limited number of actives which could cover similar use conditions as chlorophene. Attachment 1 – ED activity Assessment of the endocrine activity of chlorophene in which the applicant concludes that whereas the screening assays on endocrine activity showed some positive results, the activity was weak and therefore does not indicate a specific endocrine activity. The annex also concludes that the kidney is the main target organ of toxicity and that based on all available toxicity data chlorophene is not an endocrine disruptor. Attachment 2 - Essentiality Chlorophene 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. 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. The applicant also includes a comparison to other active substances evaluated under the BPR in PT 2 and 3 in terms of intended uses and application pattern.	LANXESS Deutschland GmbH Company - manufacturer
Tuberkulose.pdf [pc_chlorophene_non_conf_comment_06]	2	Article available on the webpage of the Robert-Koch Institut. The article from the US Center for Disease Control and Prevention (CDC) from 1994 provides guidelines for preventing the transmission of Mycobacterium tuberculosis in Health-Care Facilities. Supplement 5 (page 105 of the article, page 113 in the document) focuses on the decontamination, cleaning, disinfecting, and sterilizing of patient-care equipment,	Member State - Luxemburg

		defining the potential risk for infection associated with the equipment use.	
SV Public consultation for chlorophene PT 2 and 3.msg [pc_chlorophene_non_conf_comment_07]	2, 3	In Norway the disinfection in hospitals against organisms causing tuberculosis or aspergillosis is not considered as particularly challenging taking into account that the availability of products to be used is considered sufficient even though chlorophene is currently not on the Norwegian market. The use of phenols in Norwegian hospitals was phased out for more than 25 years ago due to the lack of efficacy towards many viruses. Due to the high dilution factor from concentrate to the in use concentration the phenol products were also considered to be vulnerable with regards to achieving the exact desirable efficacious concentration. In addition, the products were considered as rather toxic. The general rule in hospitals is that where possible, all visible contamination/organic material should be removed prior to disinfection. This applies to all the hospital disinfectants. Starting with a lower level of contamination/soiling area, one will ensure a better effect of the intended disinfection regardless of which product is used. In addition, the presence of organic material will be critical for some products, e.g. chlorine-based products, as they are inactivated in the presence of organic material. Alcohols are also not suitable in the presence of organic material, as they have insufficient abilities to penetrate such materials. Products to be used against organisms causing diseases such as tuberculosis or aspergillosis in Norway were chlorine-based products (*e.g. sodium hypochlorite n-chloro-p-toluenesulfonamide sodium salt and sodium dichloroisocyanurate dehydrate*), oxidative products (e.g. *peracetic acid, hydrogen peroxide, chlorine dioxide*) and alcohols. Some of these active substances are still in process and some are finalised, so an indication of what will be available for the prevention of tuberculosis and aspergillosis in the future could only be given after a final decision for all relevant active substances are taken.	Member State - Norway