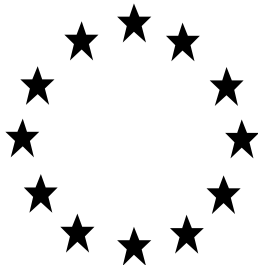
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

COMPETENT AUTHORITY REPORT

(submitted by the evaluating Competent Authority)



Silver zeolite

Product type PT 2, 4, 7

Evaluating Competent Authority:
Swedish Chemicals Agency

March 2021

Substance Name: Silver zeolite

EC Name: not asigned

EC Number: not assigned

CAS Number: 130328-18-6

Applicant: EU Silver Task Force

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1. STATEMENT OF SUBJECT MATTER AND PURPOSE

This assessment report has been established as a result of the evaluation of the active substance silver zeolite in product-type 2, 4, 7, 9, carried out in the context of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

In December 2007 (PT 2, 4 and 5) and October 2008 (PT 7 and 9) the Swedish competent authorities received a dossier from the applicant. The Evaluating Competent Authority accepted the dossier as complete for the purpose of the evaluation on 30. January 2009.

On 12. June 2017 , the Evaluating Competent Authority submitted to ECHA a copy of the assessment report containing the conclusions of the evaluation, hereafter referred to as the competent authority report (CAR). Before submitting the CAR to ECHA, the applicant was given the opportunity to provide written comments in line with Article 8(1) of Regulation (EU) No 528/2012. In 2016, PT 5 was withdrawn.

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

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of silver zeolite for product-type 2, 4 and 7 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 the assessment report, which is available from the web-site of ECHA 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. CONCLUSION

The outcome of the assessment of Silver copper zeolite product types 2 and 7 is specified in the BPC opinions following discussions at the 23. meeting (PT 2 and 7) and the 38. meeting (PT 4) of the Biocidal Products Committee (BPC). The BPC opinions are available from the ECHA web-site.

3. ASSESSMENT REPORT

Summary

1 PRESENTATION OF THE ACTIVE SUBSTANCE

1.1 IDENTITY OF THE ACTIVE SUBSTANCE

Introduction

Silver zeolite (zeolite, LTA framework type, ion-exchanged with silver and ammonium ions) is an inorganic active substance, which cannot be analysed as the complete substance. The reference specification is thus based on the concentration ranges for major elements as well as maximum levels for elements regarded as impurities.One representative active substance/biocidal product (Agion Antimicrobial Type LGK) comprised of a zeolite with a distinct level of silver is described in the dossier. The reference specification is based on this zeolite..

For silver zinc zeolite (see that CAR), the RMS concluded that the active substance should not be regarded as a'nanomaterial' as defined in the BPR. This conclusion is also confirmed for silver zeolite based on specific data (particle size data, XRD, SEM).

Main constituent(s)	
ISO name	No ISO-name assigned. The common name silver zeolite will be used throughout the report.
IUPAC or EC name	Silver zeolite (Zeolite, LTA framework type[1], ion-exchanged with silver and ammonium ions)
EC number	Not assigned
CAS number	130328-18-6[2]
Index number in Annex VI of CLP	-
Minimum purity / content	Min 99% (on a dry weight basis, based on batch data on potential impurities)
Structural formula	Not applicable

[1] The framework type is a crucial part of the identity. A silver zeolite with a different framework-type would not be considered the same substance.

[2] The CAS-No/CA-name is broader than specified by the IUPAC chemical name that is used for this entry. It has been agreed at WG V 2017 that the CAS-No/CA-name can still be used as an identifier.

Relevant impurities and additives		
IUPAC name or chemical name or EC name	**Maximum concentration in % (w/w)**	**Index number in Annex VI of CLP**
Relevant impurities Arsenic CAS-No.: 7440-38-2	Max. 26 ppm (mg/kg)	033-001-00-X
No additives		

1.2 INTENDED USES AND EFFECTIVENESS

PT 2

Use of the active substance

Product type	2
Intended use pattern(s)	Treatment of or incorporation into materials, surfaces or articles with the purpose of reducing the risk of bacterial cross-contamination. The representative biocidal product consists to 100% of the technical active substance.
Users	Professional workers. Treated articles are used by professionals and the general public, depending on the purpose of the treated item.

Effectiveness of the active substance

Function	Bacteriostatic
Organisms to be controlled	Bacteria
Limitation of efficacy including resistance	--
Mode of action	Interaction with the cell membrane, interference with electron transport processes, binding to nucleic acids, inhibition of enzymes and catalysis of free radical oxygen species.

To prevent cross-contamination, rather fast bacteriocidal effects would have to be demonstrated. The claim given by the applicant (reduces cross-contamination) and the described function (bacteriostatic) are therefore not congruent. However, the submitted tests were assessed with respect to the example uses given. For a treated article under Main group 1, the material, use-conditions and test-organisms have to be representative for at least one concrete example use. Additionally, service-life should be simulated in a tier 2 test. Efficacy under such conditions could not be demonstrated. In conclusion, approval for PT 2 cannot be suggested.

PT 4

Use of the active substance

Product type	4
Intended use pattern(s)	Treatment of or incorporation into materials, surfaces or articles with the purpose of reducing the risk of bacterial cross-contamination. The representative biocidal product consists to 100% of the technical active substance.
Users	Professional workers. Treated articles are used by professionals and the general public, depending on the purpose of the treated item.

Effectiveness of the active substance

Function	Bacteriostatic
Organisms to be controlled	Bacteria
Limitation of efficacy including resistance	--
Mode of action	Interaction with the cell membrane, interference with electron transport processes, binding to nucleic acids, inhibition of enzymes and catalysis of free radical oxygen species.

To prevent cross-contamination, a rather fast bacteriocidal effect would have to be demonstrated. The claim given by the applicant (reduces cross-contamination) and the described function (bacteriostatic) are therefore not congruent. However, one of the example use given was "Treatment of granular activated carbon (GAC) in flow-through water filters to reduce clogging and pressure" which does not represent reduction of cross-contamination, but was nevertheless accepted as a valid PT 4 use. Here, a slower bacteriostatic effect is appropriate for the purpose. For this example use, efficacy could be demonstrated successfully in a tier 2 test.
In conclusion, efficacy for PT 4 has been demonstrated for one representative use under PT 4 and approval can be suggested.

PT 7

Use of the active substance

Product type	7
Intended use pattern(s)	Protection of film against deterioration of the physical properties or appearance The representative biocidal product consists to 100% of the technical active substance.
Users	Professional workers. Treated articles are used by professionals and the general public, depending on the purpose of the treated item.

Effectiveness of the active substance

Function	Fungistatic
Organisms to be controlled	Fungi
Limitation of efficacy including resistance	--
Mode of action	Interaction with the cell membrane, interference with electron transport processes, binding to nucleic acids, inhibition of enzymes and catalysis of free radical oxygen species.

The tests provided with fungi as test-organisms could not demonstrate fungistatic efficacy for a representative PT 7 use. Thus, efficacy for PT 7 is not sufficiently demonstrated and approval cannot be suggested.

General remark

It has to be emphasized, that only a very small amount of example uses with specific materials and conditions has been tested. For the great variety of materials and use-conditions, no evaluation of efficacy can be made. There is no concept in place for PT 7 and for treated articles under PT 2 and 4, how such a great variety of uses can be evaluated. Lacking an agreed approach, the chosen way forward, to test against only one given example use, remains unsatisfactory. Most articles treated with silver zeolite will be imported into the EU, so that no additional evaluation during product authorisation will be made. Thus, the efficacy of the majority of articles on the market will remain untested. This is particularly problematical in the light of unrealistic uses and unclear purposes with the uses given in the dossier for all such silver substances which are intended to be incorporated into polymers. Even with respect to the possible risks of resistance this is a questionable situation.

Resistance

The risk of antibacterial resistance and cross resistance developing from an increased use of silver, in particular new and increasing wide-spread and disperse use in consumer products, cannot be assessed with the currently available information. Therefore, special attention should be paid to risks posed by the development of resistance/tolerance to silver and co-resistance to other relevant antimicrobial compounds at the renewal of active substance approval.

1.3 CLASSIFICATION AND LABELLING

1.3.1 Classification and labelling for the active substance

Hazard class/ property	**Proposed classification**
Physical hazards	
Explosives	None
Flammable gases	None
Flammable aerosols	None
Oxidising gases	None
Gases under pressure	None
Flammable liquids	None
Flammable solids	None
Self-reactive substances	None
Pyrophoric liquids	None
Pyrophoric solids	None
Self-heating substances and mixtures	None
Substances which in contact with water emit flammable gases	None
Oxidising liquids	None
Oxidising solids	None
Organic peroxides	None
Corrosive to metals	None
Human health hazards	
Acute toxicity via oral route	None
Acute toxicity via dermal route	None
Acute toxicity via inhalation route	None
Skin corrosion/irritation	None
Serious eye damage/eye irritation	None
Respiratory sensitisation	None
Skin sensitisation	None
Germ cell mutagenicity	None[1]

Hazard class/ property	Proposed classification
Carcinogenicity	None[3]
Reproductive toxicity	Repr 2, H361d[1]
Specific target organ toxicity-single exposure	None[1]
Specific target organ toxicity-repeated exposure	None[1]
Aspiration hazard	None[1]
Environmental hazards	
Hazardous to the aquatic environment	
Hazardous to the ozone layer	

Current Classification and Labelling according to Regulation (EC) No 1272/2008:

Classification		Labelling					
Hazard Class and Category	**Hazard statements**	**Pictograms**	**Signal word**	**Hazard statements**	**Suppl. Hazard statements**	**Precautionary statements**	**SCLs and M-factors**
There is currently no harmonised classification and labelling available for the active substance.							

Proposed Classification and Labelling *[If deviating from current classification and labelling]* according to Regulation (EC) No 1272/2008:

Classification		Labelling					
Hazard Class and Category	**Hazard statements**	**Pictograms**	**Signal word**	**Hazard statements**	**Suppl. Hazard statements**	**Precautionary statements**	**SCLs and M-factors**
Repr. 2,	H361d	GHS08	warning	Suspected of damaging fertility or the unborn child			

[3] There is no substance-specific data available for these hazard classes. Therefore, it is not possible to conclude whether or not the active substance fulfils criteria for classification. However, based on the information available for each constituent of silver zeolite, only criteria for classification Repr. 2 is anticipated to be fulfilled for the active substance. This is further discussed in the subsection of part A, section 3.

Aquatic acute 1 Aquatic chronic 1	H400 H410	GHS09		H410		P273, P391 and P501	M = 100 M = 100

1.3.2 Classification and labelling for the representative product(s)

The biocidal product consists to 100% of the active substance

Proposed Classification and Labelling according to Regulation (EC) No 1272/2008:

Classification		**Labelling**					
Hazard Class and Category	**Hazard statements**	**Pictograms**	**Signal word**	**Hazard statements**	**Suppl. Hazard statements**	**Precautionary statements**	**SCLs and M-factors**
Repr. 2,	H361d	GHS08	warning	Suspected of damaging the unborn child			
Aquatic acute 1 Aquatic chronic 1	H400 H410	GHS09	warning	Very toxic to the aquatic life with long lasting effects		P273, P391 and P501	M = 100 M = 100

Packaging of the biocidal product:

Type of packaging	**Size/volume of the packaging**	**Material of the packaging**	**Type and material of closure(s)**	**Intended user (e.g. professional, non-professional)**	**Compatibility of the product with the proposed packaging materials (Yes/No)**

2 SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT

Summary of the assessment of effects on human health

Endpoint	Brief description
Toxicokinetics	There is no substance-specific information on silver zeolite. Based on the most robust information available, a study performed with silver nitrate, it is assumed that 5% of silver ions released from AgION Antimicrobial Type LGK is orally absorbed.
Acute toxicity	Based on results from animal studies performed with a different silver zeolite, AgION Antimicrobial Type AD (see confidential section), the LD50 and LC 50 values set for acute systemic effects via oral, dermal or inhalation routes are above the acute toxicity estimates (ATE) triggering classification.
Corrosion and irritation	Results from animal studies indicate that AgION Antimicrobial Type AD causes eye irritation but the severity of effects do not fulfil criteria for classification.
Sensitisation	The result from an LLNA test performed with Agion Antimicrobial Type LGK did not indicate a skin sensitisation potential at doses up to 25% whereas results from a Buehler test in guinea pigs performed with Ag-ION Antimicrobial Type AD were equivocal. Based on theWoE, Type LGK is not expected to meet criteria for classification (see section 3.4.1.1.
Repeated dose toxicity	There is no substance-specific data available for AgION Antimicrobial Type LGK. A NOAEL for sub-chronic toxicity can be estimated if extrapolating the most conservative NOAEL set for an individual constituent of the substance to the dose of AgION Antimicrobial Type LGK needed to achieve this concentration. Using this approach, a short-term NOAEL of 21 mg/kg bw/d can be estimated based on effects noted at the LOAEL set for silver sodium hydrogen zirconium phosphate (i.e. increased level of ALP and pigmentation of the Harderian gland). This approach is further explained in section 3.6.1.1.
Genotoxicity	There is no substance-specific data available for AgION Antimicrobial Type LGK. Results obtained with silver zinc zeolite and silver copper indicate that the substances are weakly clastogenic in vitro. The negative results obtained in the follow-up in vivo chromosome aberration test is compromised by the lack of evidence for target tissue exposure. However, since a negative result was obtained in an additional follow-up study (i.e. in vivo comet assay) with silver zinc zeolite, neither silver zinc zeolite nor silver zeolite are expected to have genotoxic properties in vivo.
Carcinogenicity	There is no substance-specific data available for AgION Antimicrobial Type LGK. Considering that RAC has concluded that silver zinc zeolite (AgION Antimicrobial Type AJ) does not meet criteria for classification, AgION Antimicrobial Type LGK is not expected to have a carcinogenic potential fulfilling criteria for classification (see confidential section).

Reproductive toxicity	There is no substance-specific data available for AgION Antimicrobial Type LGK. Due to the structural similarity with silver zinc zeolite and the similarity with effects observed with other silver salts that do not contain zinc, it is reasonable to assume that silver zeolite also fulfils criteria for classification Repr. 2; H361d (Suspected of damaging the unborn child), as concluded for silver zinc zeolite.
Neurotoxicity	There is no robust information available on the neurotoxic potential of silver zeolite or any other silver containing active substance (SCAS). Considering that no effects were observed in studies with SCAS giving rise to similar silver ion exposures (based on silver content and release), there is no strong concern for a neurotoxic potential of silver zeolite. The uncertainty is considered to be compensated for by the conservative approach taken when estimating NOAELs for silver zeolite based on effect levels for individual constituents.
Immunotoxicity	There is no robust information available on the immunotoxic potential of silver zeolite. Since no strong indications of an immunotoxic potential of silver has been observed among studies performed with other SCAS, there is no strong concern for an immunotoxic potential of silver zeolite. The uncertainty is considered to be compensated for by the conservative approach taken when estimating NOAELs for silver zeolite based on effect levels for individual constituents.
Disruption of the endocrine system	The data available is insufficient to assess endocrine properties of silver zeolite. Based on the assumption that the ED potential of the substance is similar to silver zinc zeolite, the substance is not expected to meet the ED criteria. However, in line with recommendations in the guidance document, the applicant is requested to substantiate this by performing a literature review.
Other effects	Clinical reports describing cases of argyria in humans exposed to different silver substances support a human relevance of effects noted in animal studies performed with different SCAS. According to a published study performed in vitro, the inhibition by silver occurs through interference with electron transport processes, binding to DNA and interaction with the cell membrane. Results from another published study performed with silver nitrate or silver lactate indicate that perturbation of intracellular thiol homeostasis may play a crucial role in the mechanism underlying silver-induced lethal damage to isolated rat hepatocytes. None of these studies are considered to provide any mechanistic explanation for the major adverse effects observed among the toxicological studies (i.e. pigmentation of organs, increased ALP levels and histopathological changes in the liver and kidneys). However, while the first publication may only be of some relevance for the efficacy assessment, the results of the second could be considered to indicate that oxidative stress may be a contributing factor to the hepatic inflammation observed in the 90-day study in dogs.

Reference values

The rationale for the reference values in the table below is presented in part C, section 12.2.2.

Reference	Study	NOAEL (LOAEL)	AF	Correction for oral absorption	Value
$AEL_{short-term}$	If needed for risk assessment, the short-term AEL is the same as the medium-term AEL.				
$AEL_{medium-term}$	6.4.1 (04) (1995) 13 week oral rat study in rat (Crl:CDBR VAF Plus) AlphaSan RC5000 0, 30, 300 and 1000 mg/kg bw/day	21 mg/kg bw/d*	100	0.05	0.01 mg/kg bw/d
$AEL_{long-term}$	6.5 (06) (1992b) 105 week Combined chronic and carcinogenicity study in rat (F344) Silver zinc zeolite Type AJ,AgION Zeomic AJ 10N 0.01, 0.03, 0.1 and 0.3%,"at least" 0, 3, 9, 30 and 87 mg /kg bw/day)	6 mg/kg bw/d**	100	0.05	0.003 mg/kg bw/d
ARfD	Not relevant				
ADI	Not relevant				
Reference values for silver ion equivalents					
$AEL_{short-term}$	If needed for risk assessment, the short-term AEL is the same as the medium-term AEL.				
$AEL_{medium-term}$	6.4.1 (04) (1995)	0.3 (0.3) mg/kg bw/d**	100	0.05	0.15 µg/kg bw/d
$AEL_{long-term}$	6.5 (06) (1992b)	0.09 (0.3) mg/kg bw/d**	100	0.05	0.045 µg/kg bw/d
ARfD silver ion equivalents	Not relevant (no acute effects anticipated following single exposure)				
ADI silver ion equivalents	6.5 (06) (1992b)	0.09 mg/kg bw/d	100	-	0.9 µg/kg bw/d
*Estimated based on the NOAEL set for silver sodium hydrogen zirconium phosphate. **Estimated based on the NOAEL set for silver zinc zeolite.					

Risk characterisation

Summary of scenarios				
Scenario number	**Relevant product type(s)**	**Scenario**	**Primary or secondary exposure Description of scenario**	**Exposed group** (e.g. professionals, non-professionals, bystanders)
1	2, 4, 7	Mixing/loading (incl. transport, packaging and maintenance)	Primary exposure:	Industrial workers
2	2, 7	Spray application (incl. cleaning of spraying equipment)	Secondary exposure:	Professionals
3.1	2, 7	Brush and roller application	Secondary exposure:	Professionals
3.2	2, 7	Brush and roller application	Secondary exposure:	Non-professionals
4	7	Manual application of sealants	Secondary exposure:	Professionals and non-professionals
5.1	2, 4, 7	Dermal exposure to treated polymer: direct contact with human skin	Secondary exposure: Small-scale	General public
5.2	2, 7		Secondary exposure: Medium scale	
5.3	2, 7		Secondary exposure: Large-scale	
6	2, 7	Oral exposure to treated polymer: hand-to-mouth contact	Secondary exposure: Toddler or infant crawling on floor	General public
7.1	2	Oral exposure to treated polymer: taking into mouth	Secondary exposure: Small-scale	General public
7.2			A) Large-scale for infants and toddlers B) Large-scale for children and adults	General public
8	2	Oral exposure to treated textile: taking into mouth	Secondary exposure: Textile taken into mouth by infants or toddlers	General public
9.1	2	Dermal exposure to treated textile: direct contact with human skin	Secondary exposure: Large-scale	General public
9.2			Secondary exposure: Small-scale	General public
9.3			Secondary exposure: Handling of wet textile	General public

Description of exposure categories and scales used in the risk assessment for secondary (indirect) exposure as a result of use in treated articles (chapter 12.6)

Note: In order to be approved, use in a specific treated article must be acceptable both in the corresponding dermal and oral exposure category and scale.

Exposure scenario and category		**Exposure values**	
		Surface of body expected to be covered by/in contact with the article [cm²]	*Duration of contact*
Dermal exposure to treated polymer			
5 Dermal exposure to treated polymer: direct contact with human skin under wet conditions	**5.1** Small-scale	Adult: 410 Child: 214 Toddler: 115 Infant: 98 (corresponds to both hand palms)	1 min
	5.2 Medium-scale	Adult and child: 300 Toddler and infant: 200	30 min
	5.3 Large-scale	Adult: 8300 Child: 4600 Toddler: 2400 Infant: 2050 (corresponds to 50% of the total body surface, incl. head, hands and feet; exposure assessment assumes that 70% of the polymer's surface is in direct contact with skin under wet conditions; resulting in 35% of body surface exposed)	3h
Oral exposure to treated polymer			
6 Oral exposure to treated polymer: hand-to-mouth contact	Toddler or infant crawling on floor	Toddler: 115 Infant: 98 (corresponds to both hand palms; exposure assessment assumes that 40% of the polymer's surface is in direct contact with palms under wet conditions, and 50% of the substance is transferred from hand to mouth)	1h
7 Oral exposure to treated polymer: taking into mouth	**7.1** Small-scale	Adult and child: 62.8 Toddler: 31.4	5 min
	7.2 A) Large-scale for infants and toddlers	Toddler and infant: 12.6	Toddler: 1.4h Infant: 4.75h
	7.2 B) Large-scale for children and adults	Adult and child: 20	8h
Oral exposure to treated textile			
8 Oral exposure to treated textile: taking into mouth	Textile taken into mouth by infants or toddlers	Weight of article (or parts of articles expected to be taken into mouth: Toddler and infant: 1.3 g	Toddler: 1.4h Infant: 4.75h
Dermal exposure to treated textile			
9 Dermal exposure to treated textile: direct contact with human skin under wet conditions	**9.1** Large-scale	Adult: 13540 Child: 7636 Toddler: 3878 Infant: 3313 (corresponds to the total body surface except head, hands and feet) (exposure assessment assumes that 70% of the textile's surface is in direct contact with skin)	8h-24*
	9.2 Small-scale	Adult: 1130	8h-24*

Exposure scenario and category		Exposure values	
		Surface of body expected to be covered by/in contact with the article [cm²]	*Duration of contact*
		Child: 605 Toddler: 288 Infant: 246 (corresponds to surface of both feet) (exposure assessment assumes that 70% of the textile's surface is in direct contact with skin)	
	9.3 Textile handling	Adult: 410 Child: 214 Toddler: 115 (corresponds to both hand palms)	2h

* The present report contains contradicting information about the duration – 8h and 24h. The 8h was initially used for the calculation (appendix II), whereas 24h was mentioned as worst-case in the descriptions of the scenarios elsewhere in the document. This discrepancy did not influence the conclusions of the risk assessment, since the available migration data showed that silver migration has decreased to a very low rate already after 2h. Therefore, the duration did not gain further attention during the evaluation.

Summary table of main representative dietary exposure scenarios			
Scenario number	**Type of use**	**Description of scenario**	Subject of exposure
D1	Food contact materials	Migration from polymers into food (see chapter 8.7.5)	General public
D2	Preservation of water filter	Silver and ions released into drinking water (see chapter 8.7.5)	General public

Conclusion of risk characterisation for industrial user

The risk for industrial workers when mixing and loading the active substance during the formulation of polymers is acceptable if they wear appropriate respiratory protective equipment and wear protective gloves.

Task/ Scenario	**Tier**	**Systemic NOAEL** mg/(kg bw x d)	**$AEL_{long-term}$** mg/(kg bw x d)	**Estimated uptake** mg/(kg bw x d)	**Estimated uptake/ AEL** (%)	**Acceptable** (yes/no)
Scenario 1 mixing and loading	Tier 1	6	0.003	0.018[#] 0.015[¤]	603 497	No
	Tier 2 Respiratory protection (95%)			0.0098[#] 0.0097[¤]	328[#] 323[¤]	No
	Tier 2 Protective gloves (95%)			0.00915[#] 0.00597[¤]	305[#] 199[¤]	No
	Tier 2 Respiratory protection (95%) and protective gloves (95%)			0.00090[#] 0.00075[¤]	30[#] 25[¤]	Yes

[#] Inhalation assessed with MEASE model
[¤] Inhalation assessed with TNsG model 5

Conclusion of risk characterisation for professional user

PTs 2, 7: The risks for professionals when applying paints by spraying, brushing or rolling are not acceptable. Personal protective equipment is not sufficient to mitigate these risks.

PT7: The risk for professionals manually applying sealants is acceptable without personal protection, assuming that exposure is limited by the release rate of silver from the sealant.

PT 2, 4, 7: The risk for professionals handling treated articles is acceptable without personal protection, assuming that exposure is limited by the release rate of silver from the treated article.

Task/ Scenario	**Tier**	**Systemic NOAEL mg/(kg bw * d)**	**$AEL_{long-term}$ mg/(kg bw * d)**	**Estimated uptake mg/(kg bw * d)**	**Estimated uptake/ AEL (%)**	**Acceptable (yes/no)**
Scenario 2 – spray application	Tier 1	6	0.003	2.82	94052	No
	Tier 2 Hands inside gloves and body protected with overall (95% protection), 95% reduction due to use of respiratory protection			0.112	3725	No
Scenario 3.1 – brush and roll application	Tier 1			0.40	13413	No
	Tier 2 Hands inside gloves and 95% body exposure reduction using impermeable coverall			0.075	2504	No
Assessment based on silver ions						
		Systemic NOAEL mg/(kg bw * d) silver ions	$AEL_{long-term}$ µg/(kg bw * d) silver ions	Estimated uptake µg/(kg bw * d) silver ions		
Scenario 4 – joint sealant application	Tier 2 Silver migration rate	0.09	0.045	0.001	2.22	Yes

Conclusion of risk characterisation for non-professional user

The risks for non-professionals when applying paints by brushing or rolling are not acceptable.

Task/ Scenario	Tier	Systemic NOAEL mg/(kg bw * d)	$AEL_{medium-term}$ mg/(kg bw * d)	Estimated uptake mg/(kg bw * d)	Estimated uptake/ AEL (%)	Acceptable (yes/no)
Scenario 3.2 – brush and roll application	Tier 1	30	0.01	0.15	1500	No

Conclusion of risk characterisation for indirect exposure

Remark: It might appear contradictory that the risks are acceptable for all articles for oral contact (pacifiers, tooth brush, mouth guards) for all age-groups, whereas it is unacceptable for textiles for direct contact with skin for all age-groups and for even small scale items. However, this is the result of the risk assessment based on the information provided by the applicant, in line with the standard approach to address realistic worst case situations.
Obviously, refinement by - for example - providing more reliable migration data for textiles, or providing evidence that migration can be better controlled, would have been beneficial for the risk assessment.
However, the main reason for the result is that the exposed area for dermal contact is substantially larger than the orally exposed area. Since migration rates into sweat and saliva are similar and the oral and dermal absorption values are both set to 5% (based on the data provided), the exposure values for dermal contact are higher.

PT 4: The risk from indirect exposure using treated items is acceptable, assuming that exposure only will be small-scale.

PT 2, 7: The risk for toddlers or infants crawling on floor is acceptable. However, medium-scale exposure might lead to unacceptable risk for toddlers. Small scale dermal exposure does not pose unacceptable risk to humans.

Summary table: acute systemic secondary exposure of the general public								
Exposure scenario			**Tier**	**Systemic NOAEL, long-term**	**AEL, long-term**	**Estimated total uptake**	**Estimated uptake/ AEL**	**Acceptable**
				mg Ag/kg bw/d	µg/kg bw/d	µg/kg bw/d	(%)	(yes/no)
5 Dermal exposure to treated polymer: direct contact with human skin	**5.1** Small-scale	Adult	2	0.09	0.045	0.00075	1.66	yes
		Child	2	0.09	0.045	0.00098	2.17	yes
		Toddler	2	0.09	0.045	0.00126	2.80	yes
		Infant	2	0.09	0.045	0.00134	2.99	yes
	5.2 Medium scale	Adult	2	0.09	0.045	0.016	36	yes
		Child	2	0.09	0.045	0.041	91	yes
		Toddler	2	0.09	0.045	0.066	146	no
		Infant	2	0.09	0.045	0.082	182	no
	5.3 Large-scale	Adult	2	0.09	0.045	1.4	3165	no
		Child	2	0.09	0.045	2.0	4404	no
		Toddler	2	0.09	0.045	2.5	5491	no
		Infant	2	0.09	0.045	2.6	5863	no
		Toddler	2	0.09	0.045	0.015	34	yes

6 Oral exposure to treated polymer: hand-to-mouth contact	Toddler or infant crawling on floor	Infant	2	0.09	0.045	0.016	36	yes
7 Oral exposure to treated polymer: taking into mouth	**7.1** Small-scale	Adult	2	0.09	0.045	0.0006	1.3	yes
		Child	2	0.09	0.045	0.0014	3.2	yes
		Toddler	2	0.09	0.045	0.0017	3.8	yes
	7.2 A) Large-scale for infants and toddlers	Toddler	2	0.09	0.045	0.015	34	yes
		Infant	2	0.09	0.045	0.027	60	yes
	7.2 B) Large-scale for children and adults	Adult	2	0.09	0.045	0.007	16	yes
		Child	2	0.09	0.045	0.019	41	yes
8 Oral exposure to treated textile: taking into mouth	Textile taken into mouth by infants or toddlers	Toddler	2	0.09	0.045	0.062	139	no
		Infant	2	0.09	0.045	0.027	59	yes
9 Dermal exposure to treated textile: direct contact with human skin	**9.2** Small-scale	Adult	2	0.09	0.045	0.99	2203	no
		Child	2	0.09	0.045	1.33	2961	no
		Toddler	2	0.09	0.045	1.52	3369	no
		Infant	2	0.09	0.045	1.62	3597	no
	9.3 Textile handling	Adult	2	0.09	0.045	0.34	757	no
		Child	2	0.09	0.045	0.45	991	no
		Toddler	2	0.09	0.045	0.57	1275	no

Conclusion of risk characterisation for indirect exposure via food

PT 4: Based on migration data into food simulant (3% acetic acid), unacceptable risks to consumers using treated articles (including surfaces) in contact with food cannot be excluded.
The risk for consumers drinking water that has passed a filter treated with silver zeolite is acceptable for adults, children and toddlers. It is not acceptable for infants.

Summary table: indirect exposure via food						
PT 4						
Exposure scenario		**Systemic NOAEL**	**AEL**	**Estimated oral uptake**	**Estimated uptake/ AEL**	**Acceptable**
		mg Ag^+ eq/kg bw/d	µg/kg bw/d	µg/kg bw/d	(%)	(yes/no)
Migration into food simulant (3% acetic acid)	Adult	0.09	0.045	0.12-2.1	300-4580	no
	Child	0.09	0.045	0.34-5.2	752-11498	no
	Toddler	0.09	0.045	0.81-12	1798-27479	no
	Infant	0.09	0.045	1.0-15	2248-34349	no
Preservation of water filter	Adult	0.09	0.045	0.018	40	yes
	Child	0.09	0.045	0.022	49	yes
	Toddler	0.09	0.045	0.034	75	yes
	Infant	0.09	0.045	0.075	167	no

Overall Conclusion on Human Health

PT 2
The risk for industrial users is acceptable with respiratory protective equipment and protective gloves. The risk for professional users with the exemption of applying paints by spraying, brushing or rolling is acceptable. The risk for consumers applying paints by spraying, brushing or rolling is not acceptable.
The large-scale and medium-scale use of treated polymers in direct contact with skin is not acceptable. Small-scale use in polymers in direct contact with skin does not pose unacceptable risk to humans. Large-scale oral exposure (for example in pacifiers) may pose unacceptable risk to infants. The use in textiles in direct contact with skin is not acceptable, with the exemption of hand contact.
In conclusion, approval can be suggested with risk-mitigation measures.

PT 4
The risk for industrial users is acceptable with respiratory protective equipment and protective gloves. For professional users and consumers, the risk of handling small-scale treated articles is acceptable. However, the risk deriving from intake via food or drinking water by indirect exposure is not acceptable. In conclusion, approval cannot be suggested.

PT 7
The risk for industrial users is acceptable with respiratory protective equipment and protective gloves. The risk for professional and non-professional users with the exemption of applying paints by spraying, brushing or rolling is acceptable.
The risk for non-professionals applying paints by spraying, brushing or rolling is not acceptable. The large-scale or medium-scale use of treated polymer articles in direct contact with skin is not acceptable. Small-scale use in polymers in direct contact with skin does not pose unacceptable risk to humans.
In conclusion, approval can be suggested with risk-mitigation measures.

3 SUMMARY OF THE ENVIRONMENTAL RISK ASSESSMENT

Fate and behaviour in the environment

Summary table on compartments exposed and assessed - PTs 2, 4, 7		
Compartment	**Exposed (Y/N)**	**Assessed (Y/N)**
Fresh-water	YES	Yes
Sediment	YES	Yes
Sea-water	YES	The risk assessment for freshwater covers even the risk for the marine freshwater and sediment
Seawater sediment	YES	
STP	YES	Yes
Air	Negligible	No
Soil	YES	Yes
Groundwater	YES	Yes

Summary table on relevant metabolites		
Metabolite/transformation- or reaction product	**Compartment**	**% Active Substance**
Silver	Water and soil (air not relevant as it is not volatile)	Silver ions are released from treated materials to varying degree depending on use pattern and surrounding conditions. Measured release and migration data are used for the environmental risk assessment

Summary table on relevant physico-chemical and fate and behaviour parameter of silver			
	Value	**Unit**	**Remarks**
Molecular weight	107.87	g/mol	Molecular weight for elemental silver (Ag)
Vapour pressure (25°C)	1×10^{-6}	Pa	Not volatile. EUSES input value: 1×10^{-6} Pa
Water solubility (25°C)	1×10^{-3}	mg/L	Very low water solubility. EUSES input value: $1 * 10^{-3}$ mg/L
Log Octanol/water partition coefficient	-	Log 10	Not applicable to an inorganic crystalline solid which is neither soluble in water nor in organic solvents
Kp_{soil}	398.11	cm^3/g	

Summary table on relevant physico-chemical and fate and behaviour parameter of silver			
	Value	**Unit**	**Remarks**
Kp_{susp}	1.585 x 10^5	cm^3/g	a maximum value of 1 x 10^5 cm^3/g is allowed by EUSES
Fraction of emission directed to air by STP	0%		Substance is not volatile
Fraction of emission directed to water by STP	9%		Based on measured data. See silver core CAR chapter 4.1.2
Fraction of emission directed to sludge by STP	91%		Based on measured data. See silver core CAR chapter 4.1.2
Organic carbon/water partition coefficient (Koc)	-	l/kg	Not applicable to the substance itself (i.e. insoluble in water). For silver: Kd, soil-soil water = 398.11 L/kg
Henry's Law Constant (20 °C)	-	Pa/m3/mol	Not applicable to a non-volatile inorganic crystalline solid which is insoluble in water
Biodegradability	-	-	Not applicable to an inorganic compound
Abiotic degradation	-	-	Silver ions may be released under appropriate environmental conditions. The fate of the environmental relevant silver in term of its speciation in the different environmental compartments is more relevant.

Effects assessment

Summary table on calculated PNEC values	
Compartment	**PNEC**
Freshwater	0.008 µg/L (dissolved silver)
Sediment	44.1 µg/kg dry weight (9.58 µg/kg wet weight) (total silver)
Soil	5.6 µg/kg wet weight (total silver)
STP	0.009 mg/L (estimated total silver)

Exposure assessment

A summary of PEC values is presented in chapter 9.3

Risk characterization

Summary table on calculated PEC/PNEC values				
Scenario	**STP**	**freshwater**	**freshwater sediment**	**soil**
	[mg/L]	[mg/L]	[mg/kg$_{wwt}$]	[mg/kg$_{wwt}$]
2.1 – Floor covering	1.98E-06	8.92E-05	1.62E-03	0.0012
2.2 – Treated articles - service life	4.00E-06	2.13E-04	0.0039	0.0024
2.3 – Polymer formulation	4.76E-04	0.021	0.39	0.28
4.1 – Polymer formulation	4.76E-04	0.021	0.39	0.28
4.2 – Treated articles – service life	4.00E-06	2.13E-04	0.0039	0.0024
7.1.a – Polymers used on infrastructure				
CITY SCENARIO				
Sealants indoor				
application. amateur	3.83E-04	0.017	0.31	0.23
application. professional	2.30E-04	0.010	0.19	0.136
service-life. 100% leaching	8.41E-03	0.38	6.9	5.0
service-life. leaching rate	1.10E-05	4.93E-04	0.0090	0.0065
7.2 – Polymer formulation	4.76E-04	0.021	0.39	0.28
7.3 – Treated articles – service life	4.00E-06	2.13E-04	0.0039	0.0024
Aggregated exposure	*See chapter 13.7*			

Overall Conclusion for the Environment:

Sewage treatment, all PTs: No unacceptable risks to sewage treatment processes were identified for the intended uses.

Aquatic environment, all PTs: No unacceptable risks to the aquatic environment were identified for the intended uses. Silver zeolite is not incorporated into textiles or articles that are intended to be used outdoors. Therefore, outdoor applications were not assessed.

Terrestrial environment, all PTs: No unacceptable risks to soil organisms processes were identified for the intended uses. Silver zeolite is not incorporated into textiles or articles that are intended to be used outdoors. Therefore, outdoor applications were not assessed.

Groundwater, all PTs: Unacceptable risk to groundwater is not expected.

Primary and secondary poisoning, all PTs: Where risk for sediment-living organisms is acceptable, risk for predating birds or mammals will also be acceptable.

Aggregated exposure, all PTs: No risks for the environment are identified from aggregated exposure to silver zeolite, if those scenarios are considered that on their own do not show unacceptable risks either.

Note, that the exposure estimates are made based on the tonnage data provided by the applicant for the amount of biocidal product/substance placed on the EU market. This includes the product used in treated articles imported into the EU.

Aggregated exposure including other silver containing active substances will be addressed in a separate document.

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4 ASSESSMENT OF EXCLUSION, SUBSTITUTION CRITERIA AND POP

Conclusion on exclusion criteria	
Conclusion on CMR	See section 5
Conclusion on ED assessment	See section 5
Conclusion on PBT and vP/vB criteria	Not applicable to inorganic compound

Conclusion on substitution criteria	

Conclusion on LRTAP/POP assessment	LRTAP: There are no indications (monitoring data or modelling data) of any long range transport potential of the active substance. POP: Not applicable (the substance is inorganic) POP:

Part A Assessment of intrinsic properties and effects of the active substance

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

Introduction
Silver zeolite (zeolite, LTA framework type, ion-exchanged with silver and ammonium ions) is an inorganic active substance, which cannot be analysed as the complete substance. The reference specification is thus based on the concentration ranges for major elements as well as maximum levels for elements regarded as impurities.One representative active substance/biocidal product (Agion Antimicrobial Type LGK) comprised of a zeolite with a distinct level of silver is described in the dossier. The reference specification is based on this zeolite..

For silver zinc zeolite (see that CAR), the RMS concluded that the active substance should not be regarded as a'nanomaterial' as defined in the BPR. This conclusion is also confirmed for silver zeolite based on specific data (particle size data, XRD, SEM).

Summary table on substance identity	
Common name (ISO name, synonyms)	No ISO name assigned. The following common name is used in the CAR: Silver zeolite
Chemical name (EC name, CA name, IUPAC name	IUPAC-name: Silver zeolite (zeolite, LTA framework type[4], ion-exchanged with silver and ammonium ions) CA-name: Zeolites, Ag[5]
EC number	Not assigned
CAS number	130328-18-6[5]
other CAS numbers (e.g. deleted, related, preferred, alternate)	-

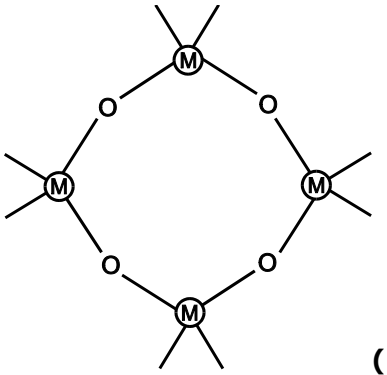
[4] The framework type is a crucial part of the identity. A silver zeolite with a different framework-type would not be considered the same substance.
[5] The CAS-No/CA-name is broader than specified by the IUPAC chemical name that is used for this entry. It has been agreed at WG V 2017 that the CAS-No/CA-name can still be used as an identifier.

Molecular formula	Generic molecular formula excluding the ratio of the elements and additional ions which are considered confidential and thus presented in the Confidential Annex: $Ag_x\ Na_y\ (NH_4)_z\ (H_2O)_m\ [Al_{12}Si_{12}O_{48}]$ **– LTA*** * Linde Type A
SMILES notation	Not applicable
Molar mass	No data available for the active substance itself. General molecular masses for zeolite type A (LTA framework type zeolite) is given in table 1.1-1 below

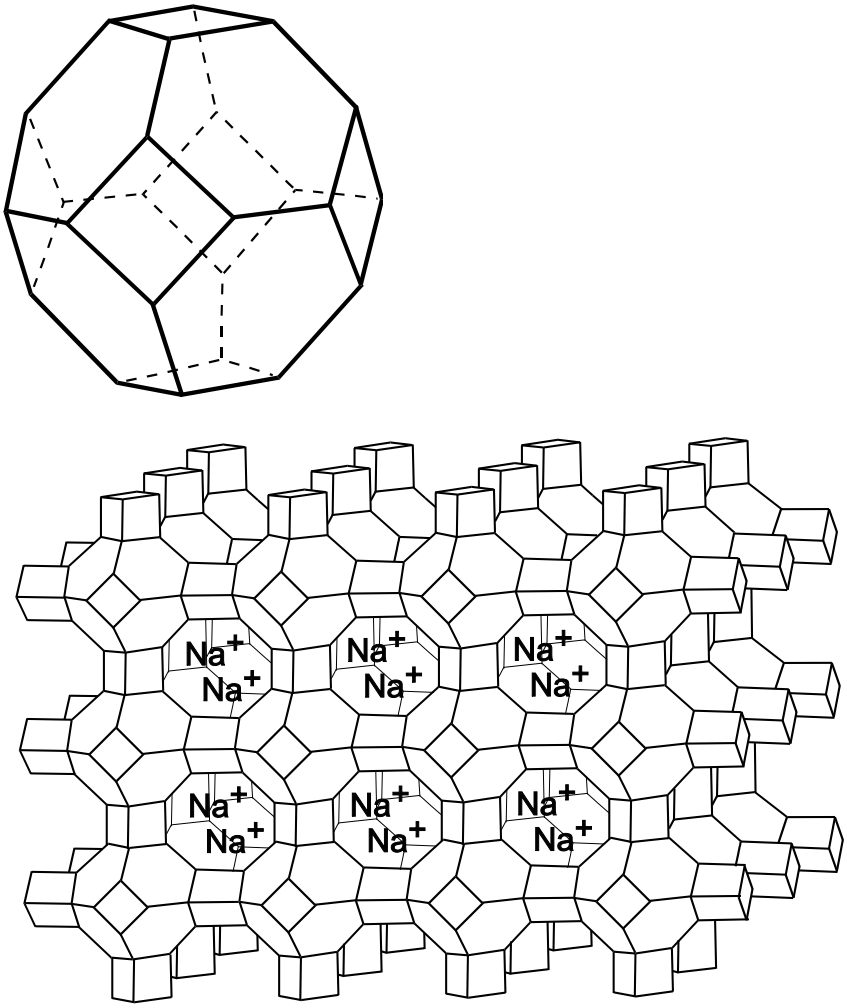
Table 1.1-1 General identity details for Zeolite A (HERA, 2005)

CAS-No.:	Specific to zeolite A: 1344-00-9 General to all synthetic zeolites: 1318-02-1
EINECS-No.	215-684-8 (CAS-No. 1344-00-9) 215-283-8 (CAS-No. 1318-02-1)
Other No. (CIPAC, ELINCS)	Not assigned
Molecular formula	General: $Na_x[(AlO_2)_x(SiO_2)_y] \times zH_2O$
Macro-molecular description (Physical State/Particle size)	Solid, three-dimensional crystalline structure (see Figure 1.1-1 below for the 2- and 3-D structure of Zeolite A) Particle size: 3-5 µm
Molecular Weight	Calculated 1: 284 [g/mol]; $Na_2O \times Al_2O_3 \times 2\ SiO_2$ (Zeolite A 4 atro)
	Calculated 2: 2190 [g/mol]; $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}] \times 27\ H_2O$
Moisture content	20-25%

Structural formula
Not applicable (see Figure 1.1-1 below for the crystal structures of Zeolite A)



(M = Si or Al)



Upper: four membered ring structural unit of the zeolite A lattice; middle: Truncated octahedron of four- and six membered rings in the zeolite A lattice; lower: Zeolite A Lattice, in Sodium Form

Figure1.1-1 Crystal structures of Zeolite A (Sciessent, 2008)[6]

Origin of the natural active substance or precursor(s) of the active substance
Not applicable

Method of manufacture
Brief non-confidential description: Silver zeolite is prepared by ion exchange of zeolite A (more detailed information is provided in the confidential Annex)

6 Sciessent, Product Properties - Part A - Zeomic® Type AC Silver Zeolite A; received as supplementary information in September 2008

1.2 COMPOSITION OF THE SUBSTANCE (REFERENCE SPECIFICATIONS)

Main constituent(s)			
Constituent (chemical name)	**Typical concentration (%(w/w))**	**Concentration range (%(w/w))**	**Remarks / Discussion**
Silver zeolite	Min 99% (on a dry weight basis)[7]	-	The reference specification is based on the levels of major elements as well as elements regarded as impurities.

Impurities			
Constituent (chemical name)	**Typical concentration (%(w/w))**	**Concentration range (%(w/w))**	**Remarks / Discussion**
Relevant impurities Arsenic CAS-No.: 7440-38-2 Information on other impurities is considered confidential (see the Confidential Annexes)	Max. 26 ppm (mg/kg)	-	-

Additives				
Constituent (chemical name)	**Function**	**Typical concentration (%(w/w))**	**Concentration range (%(w/w))**	**Remarks / Discussion**
No additives	-	-	-	-

[7] Zeolites are hygroscopic substances which naturally contains water. It has thus been agreed (WG-III; 2017) that the specification should be given on a dry weight basis.

1.3 PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

Introduction
All data and waivers used to address the phys.chem. parameters are presented in the table below. With the exception for water solubility and granulometry all data has been generated using either silver zinc zeolite or silver copper zeolite. This is in general considered acceptable given that most phys.chem. parameters are not relevant to silver zeolite due to the inorganic nature of the substance. Data on relative density is not presented but this is not considered to be a concern since this parameter is not considered crucial for the risk assessment (i.e. no further data is assumed to be required at member state level).

Water solubility with respect to the whole active substance as defined is not available (addressed with data on silver zinc zeolite). However, this is considered acceptable as silver zeolite should also be insoluble in water due to the similarities of the materials (i.e. inorgainc crystalline solids).

Water solubility data with respect to silver-ion release under various conditions is considered important for evaluating the effect levels for silver-ions, specifically in the tox-section. Such data has been provided for silver zeolite and the various other notified silver containing active substances (SCAS). As the risk assessment in the tox section for silver zeolite partly relies on read across of data for other SCAS the data is presented in full in section 1.3.1 below.

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Aggregate state at 20°C and 101.3 kPa	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: solid at 25°C	OPPTS 830-6303 (visual assessment)	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid).	Shepler (2001) IIIA 3.3.1-01
Physical state (appearance) at 20°C and 101.3 kPa	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: powder at 25°C	OPPTS 830-6303 (visual assessment)	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid).	Shepler (2001) IIIA 3.3.1-01
Colour at 20°C and 101.3 kPa	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: white at 25°C	OPPTS 830-6302 (visual assessment)	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid).	Shepler (2001) IIIA 3.3.2-01
Odour at 20°C and 101.3 kPa	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: odourless at 25°C	OPPTS 830-6304 (olfactory assessment)	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid).	Shepler (2001) IIIA 3.3.3-01
Melting / freezing point	Silver copper zeolite (Agion Silver Antimicrobial Type AC), 3.5% silver:	OECD 102 (capillary method)	No melting point is anticipated up to 360°C (max testing tem-	Cunningham (2001)

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
	No melting or decomposition ≤ 350°C		perature according to the guidance) due to the inorganic nature of the test substance. The results are considered valid also for silver zeolite given the similarities of the materials.	III A3.1.1-01
	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: No melting or decomposition ≤ 323°C			Shepler (2001) IIIA 3.3.3-01
Acidity/alkalinity[8]	Silver copper zeolite (Agion Silver Antimicrobial Type AC), 3.5% silver: pH of a 1% suspension in water was 9.1.	CIPAC Method 75	The result may not be fully representative for silver zeolite. However, it is not assumed that the pH of silver zeolite would be >10 given that the alkaline constituents are in the same concentration range as in the tested material.	Cunningham (2001) III A3.1.1-01
Boiling point at	Not relevant due to the high melting point		Valid justification	
Relative density	Relative density not addressed <u>Bulk density</u> Zeomic Type LGK Silver Zeolite A 0.5 g/cm^3	Not stated	The lack of relative density data is not considered a concern since this parameter is not crucial for the risk assessment. It was concluded in the peer-review that data from for example SDS would be acceptable. The information provided is thus considered acceptable.	EPA Statement of Formula
Absorption spectra data (UV/Vis, IR, NMR) and a mass spectrum, molar extinction at relevant wavelengths, where relevant[9]	Generally UV, IR, NMR and MS cannot be used as a means for structural identification of the substance due to the inorganic nature.		Valid justification	
Vapour pressure	Not volatile (inorganic high molecular weight crystalline solid with melting point >300 °C).		Valid justification	

[8] Parameter omitted in the new CAR template

[9] In the new CAR template granulometry is incorrectly placed in this line (i.e. granulometry is duplicated as it is also correctly placed further down in the table)

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Henry's law constant	Not applicable to a non-volatile inorganic crystalline solid which is virtually insoluble in water		Valid justification	
Surface tension	Not relevant (solubility in water is <1 mg/l and the material releases only inorganic ions in water)		Valid justification	
Water solubility at 20 °C	The active substance as such is insoluble in water. <u>Silver release</u> Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: pH5 (non-buffered): 9.2 µg/mL after 29 days. pH7 (non-buffered): 2.9 µg/mL after 11 days pH9 (non-buffered): 0.2 µg/mL after 35 days Specific data for silver release from silver zeolite and other SCAS is available and presented in section 1.3.1 below.	OPPTS 830.7840 (shake flask method) with quantification of silver by AAS	The data on silver release from the different SCAS presented in 1.3.1 indicate a very similar release kinetics between silver zeolite and silver zinc zeolite. The additional release data generated on silver zinc zeolite and presented here is thus also believed to be representative for silver zeolite.	Bussey (2001) IIIA 3.5-01
Partition coefficient (n-octanol/water) and its pH dependency Surface tension at 20 °C	Not applicable (purely inorganic crystalline solid which is neither soluble in water nor in organic solvents)		Valid justification	
Thermal stability and identity of breakdown products	Based on structure and experience in use it can be concluded that silver zeolite is thermally stable and does not form dangerous		Valid justification	

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
	substances on heating.			
Reactivity towards container material	Based on structure and experience in use it can be concluded that silver zeolite will not react with commonly used container materials.		Valid justification	
Dissociation constant	Not relevant as silver zeolite does not contain ionisable functional groups		Valid justification	
Granulometry	Agion Silver Antimicrobial Type LGK, 4-6% silver: Particle size in the particle volume distribution Mean particle size 8.4 to 9.1 µm. Min: ~0.5 µm	Laser scanning particle size measurement	Results provided in inspection certifcates. However, the results are suffcienlty reported and thus accepted.	Inspection Certificates Type LGK Doc IV **Confidential** (IIIB 3.11-01)
Viscositiy	Not relevant since the active substance is not in liquid form		Valid justification	
Solubility in organic solvents, including effect of temperature on solubility	Silver copper zeolite (Agion Silver Antimicrobial Type AC), 3.5% silver: Solubility was less than 10 g/L in the following solvents: n-heptane xylene ethyl acetate acetone n-octanol 1,2-dichloroethane Substance not expected to be soluble in organic solvents due to the inorganic nature.	CIPAC MT 181	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid). The method is for substances with solubilities >10 g/L. However, due to the properties of the substance it is anticipated to be insoluble in organic solvents.	
Stability in organic solvents used in biocidal products	Not relevant (organic solvents are not used in biocidal products containing silver zeolite and		Valid justification	

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
and identity of relevant degradation products	the substance is purely inorganic).			

1.3.1 Silver release data

Silver release data from the different SCAS' including silver zeolite is available and is presented in section 1.3.1 of the silver core CAR.

1.4 PHYSICAL HAZARDS AND RESPECTIVE CHARACTERISTICS

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Explosives	Silver zeolite complying with the generic definition does not contain any chemical groups associated with explosive properties, which is a sufficient data waiver under CLP		Valid justification	
Flammable gases	Not relevant			
Flammable aerosols	Not relevant			
Oxidising gases	Not relevant			
Gases under pressure	Not relevant			
Flammable liquids	Not relevant			
Flammable solids	The material has no capacity to initiate or support combustion; all components are inorganic and non-pyrophoric. Based on the structure and experience in use it can be concluded that silver zeolite is not flammable.		The justification is valid for all substances within the group of silver zeolites conforming to the definition in 1.1. It is an acceptable waiver for inorganic substances under CLP.	
Self-reactive substances and mixture	Data lacking		Given the nature of the substance (purely inorganic crystalline solid containing no reactive elements) it is not anticipated to be self-reactive.	
Pyrophoric liquids	Not relevant			
Pyrophoric solids	Conclusive but not sufficient for classification		Based on the nature of the substance (purely inorganic crystalline solid containing no reactive elements) and experience in use it is concluded that it is not a pyrophoric solid.	

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Self-heating substances and mixtures	LGK10T-052: Not a self-heating substance (negative results in a 25 mm and a 100 mm sample cube at 140°C)	UN Test N.4	The result is considered representative for all substances within the group of silver zeolites conforming to the definition in 1.1. The test result is sufficient to conclude that the substance should not be classified as a self-heating substance under CLP	Rivas, V. W. (2018) *IIIA 3.11-01*
Substances and mixtures which in contact with water emit flammable gases	Conclusive but not sufficient for classification		Based on the nature of the substance (purely inorganic crystalline solid containing no reactive elements) and experience in use it is concluded that it does not emit flammable gases in contact with water.	
Oxidising liquids	Not relevant			
Oxidising solids	Data lacking		Based on the fact that the material is an inorganic substance with a high melting point, containing no specific elements or complex known to confer oxidising properties, silver zeolite is not anticipated being oxidising. However, since the inorganic substance contains oxygen the waiver according to CLP does not apply.	
Organic peroxide	Not relevant			
Corrosive to metals	Data lacking		The dossier including Document III was submitted under BPD. This data point was thus not addressed. As for reactivity against container materials (see above) silver zeolite is not anticipated to be corrosive against metal.	
Auto-ignition temperature (liquids and gases)	Not relevant			
Relative self ignition temperature for solids	Data lacking		Not anticipated to self-ignite < 400°C. The material has no capacity to initiate or support combustion; all components are inorganic and non-pyrophoric.	
Dust explosion hazard	Data lacking		The dossier including Document III was submitted under BPD. This data point was thus not addressed. However,	

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
			since silver zeolite appears to fulfil the waiving critreria (i.e. inorganic substance that cannot be oxidised), it should be exempt from testing.	

1.5 HAZARD IDENTIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Silver zeolite is the assigned generic name for zeolites (sodium alumino silicate), in which sodium-ions have been exchanged with silver and additional ammonium ions (see the Confidential Appendix for the exact composition of the representative silver zeolite). Based on the nature of the substance it can be concluded that silver zeolite is not flammable, explosive or oxidizing and that it is not reactive towards packaging material. Based on data on Agion Antimicrobial Type LGK it is concluded that the substance is not self-heating.

Hereby, there are no hazards identified based on the physico-chemical properties of the representative silver zeolite included in this CAR or for a hypothetical silver zeolite conforming to the generic identity details given in Section 1.

1.6 ANALYTICAL METHODS FOR DETECTION AND IDENTIFICATION

Introduction

In the new CAR-template for BPR, in part A section 1.6 there is only a table included named analytical methods. However, in part B section 6.5 there is a table included which is named analytical methods for monitoring as well as separate tables named analytical methods for soil, water, air etc. This appears to be inconsistent and incorrect. The RMS assumes that in Part A, the analytical methods for the active substance as manufactured as well as methods for monitoring of the active substance in the different matrices should be listed. Furthermore , in part B, only methods for the active substance in the representative biocidal product and any methods required for monitoring of relevant components of the biocidal product in the different compartments should be listed. This would be in line with the data requirements in BPR.

The RMS has thus used this approach rather than following the new CAR template for these sections.

Evaluation

1. Analysis of the active substance as manufactured

It is not possible to analyse the active substance as such. Instead methods are provided for the determination of silver and other major components and for the determination of potential impurities, among them heavy metal impurities in the active substance as manufactured. The methods as listed in the table below have been used to derive batch data on representative material and are considered acceptable.

2. Analytical methods proposed for monitoring.

It is not relevant to monitor the active substance as such in the different compartments as no such analytical methods exists and/or as the intended use in treated articles means that silver zeolite as such will not reach the different compartments.

Instead, silver being the biocidal active element, is considered to be the relevant residue to be monitored in the different compartments. The methods proposed for monitoring of silver are listed in the Section 1.6 of the silver core CAR.

It should be noted that methods for air and animal and human fluids and tissues are not considered required as none of the constituents of the active substance are volatile (and is not used in spraying applications) and as silver zeolite is not considered toxic or highly toxic.

Since the intended use includes treated articles in contact with food (PT 4), an analytical method for food and feeding stuffs was provided in the dossier. The method, based on ICP-oa-TOF-MS, was taken from the open literature and does not contain the level of validation data normally required. However, during the technical expert discussions for silver zinc zeolite (WG III 2015 APCP 6.1) it was concluded that no further data was required for this method (i.e. MRL for silver in food or feeding stuffs is currently not warranted).

3. Additional methods for relevant matrices taken from the open literature

The RMS communicated during the evaluation that analytical methods for determining silver in sediments and sewage sludge and for the determination of free silver ions (Ag^+) in environmental waters should be provided due to the use pattern andthe highly adsorptive properties of silver. Furthermore, it seems from the fate and ecotox section that free Ag^+ is the most toxic species and that this species may not be present in environmental waters. To address this, the applicant provided several methods from the open literature which are listed and discussed in section 1.6 of the silver core CAR..

Analytical methods for the analysis of the active substance as manufactured including impurities and impurities									
Analyte (type of analyte e.g. active substance or impurities)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	Mean	RSD		
Silver and other main components and potential (heavy metal) impurities.	Full dissolution/digestion in a mixture of HF/HNO_3 (1:4) followed by analysis with ICP-OES	4% (main elements) 100 ppm (remaining elements)	The tested linearity range for main components was 0.02-2.0 ppm. Remaining elements were tested in the range of 0.004-1.0 or 0.02-0.5 ppm. Correlation coefficient 1.0 for all elements tested.	ICP-OES is a specific method as all elements are determined at a unique wavelength.	Mean range: 89-126	Not relevant	0.2-5.6%	LOD: 4 ppm (As, Cd, Cr) 20 ppm (remaining elements)	Drinkard, P. (2016) Confidential Annex

Analytical methods proposed for monitoring in soil										
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**LOQ reuired**	**Reference**
					Range (n=5)	**Mean**	**RSD**			
silver	See Silver Core CAR, section 1.6									

Analytical methods proposed for monitoring in air									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**LOQ reuired**	**Reference**
					Range (n=5)	**Mean**	**RSD**			
Not relevant – no constituents of the active substance is volatile and it is not used in spraying applications.										

Analytical methods proposed for monitoring in water									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**LOQ reuired**	**Reference**
					Range (n=5)	**Mean**	**RSD**			
silver	See Silver Core CAR, section 1.6									

Analytical methods proposed for monitoring in human body fluids and tisues									
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**LOQ reuired**	**Reference**
					Range (n=5)	**Mean**	**RSD**			

Not required – The active substance is not proposed to be classified as toxic or highly toxic

Analytical methods proposed for monitoring for residues in food and feeding stuff										
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**LOQ reuired**	**Reference**
					Range (n=5)	**Mean**	**RSD**			
silver	See Silver Core CAR, section 1.6									

Additional analytical methods from the open literature for the analysis of silver in relevant compartments										
Sewage sludge										
Analyte (type of analyte e.g. active substance)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**LOQ reuired**	**Reference**
					Range (n=5)	**Mean**	**RSD**			
silver (total)	Sludge is acid-digested with HNO_3 and homogenized. The extract is analyzed for silver graphite furnace AAS (GFAAS) at 328.1 nm.	No data	Calibration range reported as 0.002-0.03 mg/l (not clear if it relates to the sludge or to the injected extract)	The analysis is specific to silver, but of course not specific to silver originating from the use of silver zeolite.	-	-	4.9	LOD= 2 µg/l	-	Sterrit & Lester, 1980 III A4.2-03

2 EFFECTS AGAINST TARGET ORGANISMS

2.1 FUNCTION AND FIELD OF USE ENVISAGED

Silver zeolite will generate the Ag^+ ion *in-situ* during use. The Ag^+ ion is a bactericide and fungicide effective against a broad spectrum of microorganisms (e.g. Gram positive and Gram negative bacteria, fungi and yeasts).

Silver zeolite is intended for use as a biocide within the following product type areas:

Main Group 1: Disinfectants and General Biocidal Products

PT2	Private area and public health area disinfectants
PT4	Food and feed area disinfectants

Main Group 2: Preservatives

PT7	Film preservatives

Silver zeolite is typically incorporated into polymers where the release of Ag^+ ions can exert a biocidal effect during use of the polymer in treated articles. Incorporation and conditions of use have a huge impact on efficacy. The representative biocidal product is AgION® Silver Antimicrobial Type LGK.

Efficacy data specific to the use of silver zeolite is summarised in Part B, chapter 7 and in Document IIIB 05.

2.2 INTENDED USES

Summary table of intended use(s) PT 2	
Problem description	Surfaces/materials contribute to cross-contamination with pathogens
Intended use pattern(s)	Treatment of or incorporation into materials, surfaces or articles with the purpose of reducing the risk of bacterial cross-contamination.
Organisms to be controlled	Bacteria
Function	Bacteriostatic
Claimed effect	1. Killing on contact 2. Inhibition of growth
Mode of action	Interaction with the cell membrane, interference with electron transport processes, binding to nucleic acids, inhibition of enzymes and catalysis of free radical oxygen species.
Products/organisms/objects to be protected	Humans against pathogens

Summary table of intended use(s) **PT 2**	
In which matrix is the product used?	Polymers: e.g. Polyvinylchlorid (PVC), Acrylonitrile Butadiene (ABS), Polypropylene (PP), High impact polystyrene (HIPS) - polyethylenes and styrenes are the most common types
Concentration of product in the material/articles	Silver zeolite is incorporated into polymers and coatings at a maximum level of 5.0% by weight, delivering up to 0.25% silver in the end-use treated articles.
Concentration of active substance in the in-use formulation/product	The product consists to 100% of the active substance; silver content range: 4% to 6%
Example uses given by the applicant:	1. Wall or floor covering 2. Air conditioning components where control of bacteria is necessary to maintain hygiene.
How fast will the product in its matrix produce the effect?	Not given.
The duration of the effect (residuality) in the matrix or lifespan of the treated article	Long term effect specific to treated article and conditions
Wet state of the matrix the product is used in	Type LGK is incorporated into a solid matrix
Wet state of the use conditions of the article	Humid conditions. Intended areas of use present conditions that are conducive to bacterial growth
Resilience/resistivity towards ageing, weathering or other use conditions as for instance washing	Indoor use only Treated articles will be washed only infrequently, or likely not at all.
Leaching/migration data for different materials or different use conditions if relevant for efficacy	Leaching depends on many different factors; please see chapter 9.2.1.
Field of use (indoors/outdoors)	The treated polymers can be used to make consumer items where an antimicrobial effect is desirable, for example: walls and flooring, heating, ventilation and air conditioning equipment, protective covers, waste containers, plumbing equipment (for example toilet seat or bathtub), office equipment and personal care items.
Category(ies) of user(s)	The incorporation of silver zeolite is performed industrially by professional users. The end-use items may be used both by professional workers and the general public (non-professional), depending on the purpose of the treated item or coating.
Instruction for use	Not given.

Summary table of intended use(s) **PT 4**	
Problem description	Surfaces/materials which come into contact with food contribute to cross-contamination with pathogens
Intended use pattern(s)	Treatment of or incorporation into materials, surfaces or articles with the purpose of reducing the risk of bacterial cross-contamination.
Organisms to be controlled	Bacteria
Function	Bacteriostatic
Claimed effect	1. Killing on contact, 2. prevention of bacterial growth
Mode of action	Interaction with the cell membrane, interference with electron transport processes, binding to nucleic acids, inhibition of enzymes and catalysis of free radical oxygen species.
Products/organisms/objects to be protected	Humans against pathogens.
In which matrix is the product used?	Granular activated carbon (GAC), Polymers: e.g. Polyvinylchlorid (PVC), Acrylonitrile Butadiene (ABS), Polypropylene (PP), High impact polystyrene (HIPS) - polyethylenes and styrenes are the most common types
Concentration of product in the material/articles	Silver zeolite is incorporated into polymers and coatings at a maximum level of 5.0% by weight, delivering up to 0.25% silver in the end-use treated articles.
Concentration of active substance in the in-use formulation/product	The product consists to 100% of the active substance; silver content range: 4% to 6%
Example uses given by the applicant:	1. i) food packaging ii) food containers, tubing iii) food processing equipment iv) food utensils. 2. Treatment of granular activated carbon (GAC) in flow-through water filters to reduce clogging and pressure
How fast will the product in its matrix produce the effect?	Not given.
The duration of the effect (residuality) in the matrix or lifespan of the treated article	Example use 1: No information given Example use 2: Filter life about 9500 liters flow-through
Wet state of the matrix the product is used in	Type LGK is incorporated into a solid matrix
Wet state of the use conditions of the article	Dry/Wet (Example uses 1)/Wet (Example use 2)
Resilience/resistivity towards ageing, weathering or other use conditions as for instance washing	Indoor use only Treated articles may be washed.

Summary table of intended use(s) **PT 4**	
Leaching/migration data for different materials or different use conditions if relevant for efficacy	Leaching depends on many different factors; please see chapter 9.2.1.
Field of use (indoors/outdoors)	Incorporation into polymer treated articles, for example - packaging, gaskets, general purpose containers, food and drink containers, food trays and covers, sponges, plastic film, food wrap, tubing, brush bristles, liners, non-woven fabrics, appliances and equipment, kitchen utensils, cutting boards, counter tops, sinks, tiles, dishes, cups, bottles, conveyer belts, food and drink processing equipment. Treatment of granular activated carbon
Category(ies) of user(s)	The incorporation of silver zeolite is performed industrially by professional users. The end-use items may be used both by professional workers and the general public (non-professional), depending on the purpose of the treated item or coating.
Instruction for use	Not given.

Summary table of intended use(s) **PT 7**	
Problem description	Biodeterioration of surfaces
Intended use pattern(s)	Protection of film against deterioration of the physical properties or appearance
Organisms to be controlled	Fungi
Function	Fungistatic.
Claimed effect	Prevents fungal growth.
Mode of action	Interaction with the cell membrane, interference with electron transport processes, binding to nucleic acids, inhibition of enzymes and catalysis of free radical oxygen species.
Products/organisms/objects to be protected	Coatings: e.g. acrylic coated Al and directly coated stainless steel.
In which matrix is the product used?	Polymers or other materials
Concentration of product in the material/articles	Silver zeolite is incorporated into matrices at a maximum level of 5.0% by weight, delivering up to 0.25% silver in the end-use treated articles.
Concentration of active substance in the in-use formulation/product	The product consists to 100% of the active substance; silver content range: 4% to 6%
Example uses given by the applicant:	1) Laminated work surface 2) Paint finish

Summary table of intended use(s) **PT 7**	
How fast will the product in its matrix produce the effect?	No information given.
The duration of the effect (residuality) in the matrix or lifespan of the treated article	No information given.
Wet state of the matrix the product is used in	Type LGK is incorporated into a solid matrix - coating
Wet state of the use conditions of the article	Humid conditions. Intended areas of use present conditions that are conducive to fungal growth.
Resilience/resistivity towards ageing, weathering or other use conditions as for instance washing	Indoor use only Treated articles will be washed only infrequently, or likely not at all.
Leaching/migration data for different materials or different use conditions if relevant for efficacy	Leaching depends on many different factors; please see chapter 9.2.1.
Field of use (indoors/outdoors)	In protective finishes exposed to humidity which are prone to fungal growth, such as: Polymer based coatings, films and laminates for non food contact uses: for example, walls, wallboard, floors, roofing, shingles, industrial equipment, furniture, vehicle parts, packaging, paper products, barrier fabrics, glazing for tiles and vitreous china, air conditioning, heating and ventilation equipment. Adhesives and sealants for non food contact uses: for example, adhesives used in wood and plastic manufacture, adhesives for tiles, wood, paper, cardboard, rubber and plastic, glazing for windows, grout, pipe sealant, adhesives, sealants and insulation used in bathrooms and other construction.
Category(ies) of user(s)	The incorporation of silver zeolite is performed industrially by professional users. The end-use items may be used both by professional workers and the general public (non-professional), depending on the purpose of the treated item or coating.
Instruction for use	Not given.

	1.

2.3 SUMMARY ON EFFICACY

2.3.1 Efficacy

The applicant has not submitted experimental data for the active substance silver zeolite. The antimicrobial properties of silver zeolite are based on release of ionic silver from the zeolite structure. Thus, the applicant refers to the general antimicrobial properties of silver ions. To substantiate this, the applicant refers to published literature. More specific information on silver zeolite, including experimental data, can be found in Part B.

Silver ions

Silver has a broad spectrum of activity against bacteria and fungi (including yeasts). A large body of published data exists that confirm the efficacy of silver against these organisms and a selection of these data are summarised in Document IIIA, Section 5. In the studies presented, effectiveness was confirmed against a number of Gram-positive and Gram-negative bacteria, yeast (*Candida albicans*) and mould (*Aspergillus niger*). The biocidal effects of silver ions, released electrolytically, were tested, but also of silver salts like silver chloride and silver nitrate and silver compounds such as silver zinc zeolite. In addition, the biocidal effects of different silver containing active substances (SCAS) incorporated into materials were tested, such as polymers or metal with silver incorporated or coated onto the material. If possible, the observed effect was quantified in relation to dissolved silver. In each case, the biocidal effect was attributed to the presence of dissolved silver in situ. In one study (IIIA 5.3.1-01c, Mavilia 1999) the effect could be attributed explicitly to free silver ion.

Different test conditions were applied and different endpoints were investigated in the presented studies, thus severely limiting the comparability between studies. Minimum effective silver concentrations were found to be in the range of 30 to 30 000 µg/L. Generally, silver showed the highest efficacy against Gram-negative bacteria followed by Gram-positive bacteria followed by *C. albicans* and *A. niger*. Materials with incorporated or coated silver had the ability to inhibit microbial growth. The formation of biofilm was inhibited, but bacteria are more resistant once a biofilm is established. The efficacy against viruses has not been proven sufficiently.

Silver incorporated into polymers

Generally, the antimicrobial effect of silver containing active substances (SCAS) incorporated into (polymer) materials is dependent on how much of the silver is released. A precondition for the release of silver is a solvent, i.e. a liquid which the material comes into contact with. **A dry (polymer) material surface will likely not release sufficient silver ions and thus will not exert an antimicrobial effect.** Given the surface is in contact with a solvent, the release is additionally modulated by other factors, such as surface area of the (polymer) material, contact time with the solvent, ionic strength of the solvent and on the type and amount of the SCAS incorporated. In addition, different polymers have different water absorption characteristics; the greater the tendency of a plastic to absorb moisture, in theory the more silver will be released (see also chapter 9.2.1). Thus different polymer materials will show different efficacy even with the same silver loading.

Silver zeolite is used exclusively for incorporation into different materials.

2.3.2 Mode of action

Please refer to the silver core dossier.

2.3.3 Resistance

Please refer to the silver core dossier.
At the renewal of active substance approval, special attention should be paid to risks posed by the development of resistance/tolerance to silver and co-resistance to other relevant antimicrobial compounds.

2.4 CONCLUSION ON EFFICACY

Silver has long been known as a biocide with a broad spectrum of activity against fungi and bacteria. MICs vary from 30 – 30 000 µg/l. The uses applied for are exclusively in materials in which silver zeolite has been incorporated, either directly into the polymer-matrix, or by incorporation into a coating and subsequent application of the coating. The availability of silver from these materials is hugely dependent on different factors, the most crucial of them being the presence of a solvent. Without a solvent that the treated material comes into contact with, no silver will be released and no antimicrobial effect will be achieved. Thus, the environmental conditions the treated material is used in, have a huge effect on efficacy. Due to the variability of uses for the materials treated, it is difficult to judge whether conditions will be favourable to trigger release of silver.

Unspecific claims and PT-allocations

The claims originally submitted for silver zeolite were so unspecific ("to make items where an antimicrobial effect is desirable") that it was impossible to prove them right or wrong. Together with these unspecific claims, a list of possible applications per PT was given, (see

2.2 in the summary table on intended uses, row "field of use"; furthermore, in Doc III A 5.5 and in Doc IIIB 5.1.2). However, it often remained unclear what the purpose of the antimicrobial treatment for the different items was and specifically, whether it was the items or humans which were to be protected. Additionally, it was not always clear against what the items or humans were to be protected, or in other words, what the detrimental effect of the microorganisms was. Thus, the applicant was requested to provide clearer problem descriptions, claims and example uses, which they submitted (see document "Efficacy information silver zeolite"). However, even these more precise claims and example uses submitted sometimes needed translation into categories which could be demonstrated. Also, in case the allocation of the submitted tests to PTs and example uses was lacking, the eCA allocated them to suiting PTs and uses, mainly based on the test organisms and use-conditions employed in the tests. Also the materials tested were taken into account. Thus, the evaluation of the tests was carried out with respect to the example uses given.

The significance of use-conditions for efficacy

As silver zeolite is exclusively used to treat (mostly polymer) articles, it is difficult to deal with the great variety of possible uses. However, efficacy is highly dependent on use conditions, crucially the availability of humidity, and on the material the silver zeolite is incorporated into. Tier 1 tests should reflect a certain set of use conditions; conclusions can only be drawn with respect to these use conditions, or at least a set of comparable use-conditions (e.g. tests on hard surfaces with contaminants applied in small droplets which dry out at room temperature can be used to evaluate different hard-surface applications, provided the material has a similar release pattern and the claim is the same). Tier 2 tests, in addition, should give information about the duration of the effect under realistic in-use conditions. (In the aforementioned example, if these hard-surfaces are used indoors, weather, wind and UV-radiation probably don't play a role, and so the release of the active substance over the time tested could be extrapolated to the possible life-time of the article or material, taking cleaning regimes into account). This could possibly be even extrapolated to other materials with a similar release pattern.

For the assessment of actives used in a great variety of treated articles/materials, there is no common practice in place how to deal with this variety. Only for wood-preservatives, methods have been developed over time which take a variety of use-conditions into account. In contrast to treated wood, however, treated polymers are more likely to be imported into the EU, without the additional step of product authorisation. Even if product authorisation would take place, the methodological difficulties to assess a great variety of use conditions remains. The way forward can only be the creation of use- and exposure categories as it is common practice for wood-preservatives, but also for the assessment of industrial chemicals under REACH.

As long as there is no consensus amongst MSs and the Commission how to deal with such variety of uses on active substance level, as a minimum requirement, one representative example use per claim and PT should be given and efficacy should be demonstrated at least with tier 1 and tier 2 level tests for this example use.

PT 2

For the function described (reduce bacterial cross contamination), rather fast bacteriocidal effects would need to be demonstrated. An additional difficulty, represented by example use 1 (Wall or floor covering), are the dry use-conditions which make it difficult for the silver ions to be released. None of the submitted tests represents such use-conditions (splash contamination in otherwise dry surroundings).

For example use 2, an inhibition of growth claim can be assumed. Inhibition of growth for different materials and different bacteria under wet conditions have been demonstrated in a tier 1 test. However, disinfectants for air-conditioning systems are normally applied by airborne diffusion of an aerosol, a smoke, a vapour or a gas. It would need to be shown

with appropriate tests that this function can be fulfilled even by a biocide incorporated into the parts of an air-conditioning system. Such tests have not been provided. In conclusion, efficacy for PT 2 applications is not sufficiently supported.

PT 4
The examples given for PT 4 (i) food packaging, ii) food containers, tubing, iii) food processing equipment, iv) food utensils) are very unspecific; therefore, it is difficult to tell which effects would be required.
In case that fast bacteriocidal effects would be required in uses to reduce cross-contamination, the studies submitted are evaluated against this assumption. However, in none of the studies conditions to support this scenario are applied (splash-contamination in a rather dry surrounding and rather fast effects would have to be demonstrated).
In other cases, growth-reduction might be a sufficient effect for food-contact materials, though the description "reduces cross-contamination" does not really comprise such uses. However, as one study representing a reduction of growth scenario was submitted, this claim was assumed to be made, though not explicitly stated. A granular activated carbon(GAC) in a flow-through water filter was treated to reduce clogging and pressure. For this example use, efficacy has been demonstrated in a simulated use (tier 2) test.
However, conclusions on applications in static water-filters (post-tap) or conclusions on the efficacy of other food contact materials where prevention of growth is claimed cannot be made. Representative examples of such uses would have to be tested specifically.

PT 7
The tests submitted which employed fungi as test organisms, did not demonstrate efficacy for a representative use under PT 7 due to lack of growth in untreated materials and due to materials employed which were not representative for the example uses. In conclusion, efficacy for PT 7 applications is not sufficiently supported.

3 ASSESSMENT OF EFFECTS ON HUMAN HEALTH

Description of the data submitted: The dossier received from the (European) Silver Task Force ((E)STF) is a joint dossier that originally included nine different silver containing active substances (SCAS) notified in the review programme: elemental silver, silver chloride, silver glass, silver sodium hydrogen zirconium phosphate, silver zeolite A, silver zinc zeolite, silver nitrate and disilver oxide. During the evaluation process, the eCA questioned the identity set for some of the SCAS. In response to questions raised by the eCA, the (E)STF revised the identity of the substances. Based on the chemical composition, the SCAS were redefined and silver zeolite became a separate entry.
The hazard assessment presented in the original dossier was compiled from data available for the different SCAS and this hazard assessment and the reference values derived were considered applicable to all the different SCAS reviewed. However, due to several uncertainties with the read-across proposed (see below), the eCA proposed to present separate hazard assessments for each of the SCAS as this was considered more appropriate, both from a scientific point of view and for fairness.
It should be noted that since the representative product, Agion Antimicrobial Type LGK, consists of 100% active substance, professional use means handling of the active substance and a substance-specific hazard assessment is thus also needed. The hazard assessment made is, as far as possible, based on substance-specific data and read-across to information available for a different SCAS has only been applied in case data gaps are identified for certain endpoints. The (E)STF has agreed to this as a general approach and separate reports are thus prepared for each individual SCAS.
Doc IIIA contains the study summaries of all information submitted for the different SCAS and is regarded as a database of experimental studies, literature data, expert statements and published research from which information for a certain SCAS can be obtained.
Use of data for different SCAS:
There is no complete toxicological data set available for any of the SCAS. The applicant claims that data gaps for a certain SCAS can be filled by results obtained with a different SCAS or by data available in the open literature. The basis for this type of read across is that the silver ion which is released from all SCAS should be regarded as the active biocidal substance. The applicant has thus adjusted the no observed adverse effect levels (NOAEL) set for different SCAS with respect to silver content in order to set a (NOAEL) for the silver ion. These adjusted NOAELs are then considered for point of departure in the derivation of reference values which the applicant considers applicable to all SCAS under review.
The RMS does not fully agree with this approach since it is complicated by the SCAS and the different sub-types of SCAS having different chemical, physical and possibly also toxicological properties. They may not only differ due to potential toxic effects of the carrier molecule but also with respect to the actual amount of silver ions (and other metal ions) released. While it may be possible to identify a "worst case carrier" and use data obtained for this substance as a "worst case" for other SCAS, it is more difficult to manage differences in silver release. The rate of release may have a significant impact on the silver concentration actually exposed to in the toxicological studies performed. If assuming, as proposed by the applicant, complete silver release from the SCAS and the fraction released in fact is lower, the true effect level of silver ions could be under-estimated. Therefore, in case the NOAEL is set based only on silver content in the SCAS without taking into account the release, there is a concern that this NOAEL may not ensure protection from adverse health effects when applied to a different SCAS having a similar silver content but a higher silver release.
Nevertheless, in order to use the existing data for the hazard assessment of the different SCAS, the applicant was asked for substance-specific data on silver release during conditions assumed to mimic physiological conditions. This was considered an acceptable approach to overcome the uncertainty regarding silver ion release without having to request

further animal testing. The results of this study (presented in table 1.3.1-4 of the core dossier) show a silver release varying between 2 and 42% of the maximum silver content of the different SCAS after 12 hours[10] when tested at pH 4, 37°C, i.e. conditions assumed to represent those of the the rat stomach and intestine. From this release data, the actual exposure to silver ion equivalents in the different studies has been calculated to set NOAELs for silver ion equivalents. Thereafter, a NOAEL for silver zeolite has been estimated by calculating the dose needed to achieve the same silver ion exposure. This approach is assumed to be conservative since all effects are ascribed to the silver ion although other constituents of the SCAS tested (e.g. copper, zinc, zirconium) may contribute to the toxicity. Since the objective in this report is to assess the toxicological hazard and risk from silver zeolite and silver ion equivalents, any data gap identified for the other SCAS will not be addressed in this report.

Literature data:

Silver and different silver compounds have been used for many years in areas such as health care, jewellery and in the photo industry. Therefore, there is a huge amount of information and published research on silver available in the open literature. Literature data account for a relatively large part of the total data in Doc IIIA and include expert summaries, published research, chapters or extracts from different textbooks as well as reports made by regulatory authorities such as the US EPA (U.S. Environmental Protection Agency) and ATSDR (Agency for Toxic Substances and Disease Registry). Even though this data provide a lot of useful information, the majority of the studies cited is old and the quality of the studies cannot be assessed without access to original data. Therefore, these documents are generally regarded as supplementary information only. However, in case a publication referred to has been considered to add crucial information on a certain endpoint, the original publication has been requested from the applicant and evaluated in an addendum to the toxicological section of Doc. IIIA. Many of the statements and summaries included have been prepared by experts engaged in the European Silver Task Force. This data is also regarded as supplementary information only.

Hazard assessments of silver ions:

Consumers will be exposed to silver ions released from treated articles rather than to the active substance. For accuracy and to facilitate for assessments of the cumulative exposure resulting from biocidal uses of different SCAS, the exposure to silver ions during different scenarios should be compared to a reference value set for the silver ion equivalents. Unfortunately, the dossier does not contain any studies performed with a soluble silver salt to investigate effects of free silver ions in solution. Instead, the effects of silver ions have been tested, to some extent, indirectly through studies with SCAS releasing silver ions in the gastrointestinal tract. Hence, the toxicological studies performed with different SCAS form a data base from which a hazard assessment of the silver ion equivalents can be made. All toxicological data submitted is thus reviewed in Doc IIIA and no observed adverse effect levels in mg SCAS/kg bw are converted into estimated doses of silver ion equivalents based on silver content and release ($NOAEL_{SCAS}$ x silver content (%) x silver ion release (%)).The reference value is then derived from the NOAEL considered most relevant, the amount of oral absorption and an appropriate safety factor.

10 The time-point was chosen by the applicant based on the following justification:
"In order to compare the behaviour of the silver active substances following ingestion, the likely residence time in the alimentary canal needs to be considered. This time is relatively short; in the human typically 2 to 2.5 days and in the rat 1 to 1.5 days. Refining this further for the rat, the time in the stomach is typically 6 hours with a worst case residence time of 12 hours, and in the intestine a residence time of 12 to 18 hours is likely, with 18 hours the worst-case."

To highlight that the NOAELs set for silver ions are estimated from tests performed with different SCAS rather than being true NOAELs for silver ions, the term NOAEL"silver ion equivalents" is used instead of "silver ion" throughout this report.
The "silver ion equivalent" concept is thus a tool for assessing risks following exposure to silver ions released from treated articles without any contribution from the other elements in the SCAS. Even though this may overestimate the effect level, it is considered to be a reasonable strategy to compensate for the lack of data on ionic silver. Moreover, the effect commonly seen at the NOAELs for different SCAS is pigmentation, an effect regarded as a silver-specific.
Nevertheless, the effect levels set for the silver ion equivalents should neither be regarded as true effect levels for silver ions nor be used for the purpose of classification.

Batches used in toxicological studies:

Full impurity profiles of batches used in the studies performed with silver sodium hydrogen zirconium phosphate or silver zinc zeolite (read across for carcinogenicity) are not available. However, this lack of information is not considered to justify conducting further studies since maximum levels for impurities of possible concern (i.e. heavy metals) can yet be set based on established reference values (see confidential document on the reference specification).

3.1 TOXICOKINETICS

The section on toxicokinetics is mainly based on data available in the open literature. In order to clearly illustrate the underlying data, all documents submitted are listed in the table below, irrespective of the reliability of the results or of their relevance for this assessment.

Summary table of toxicokinetic studies					
Method **Guideline, GLP status,** **Reliability**	**Species,** **Strain,** **Sex,** **No/Group**	**Test substance,** **Dose levels** **Duration of exposure**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
Oral Summary of literature data. Articles referred to as original sources of information: Shavlovski et al. (1995) Linder (1991) Linder (2002) and ATSDR (1990) citing the following published research:			10-20% absorption of silver in mammals Silver is excreted in the bile by a first-pass route and to a large extent as a glutathione conjugate	Reliability 3	IIIA 6.2(01) [redacted] (2007)
Oral Furchner, J.E, Richmond, C.R. and Drake, G.A. (1968) Evaluated in IIIA 06 Silver Addendum 1 Reliability 2-3	mouse/rat/monkey/ dog	Silver nitrate, Dose unknown single exposure	Mouse and monkey: biexponential excretion profile with biological half-lives of 0.1 and 1.6 days in mouse and 0.3 and 3 days in monkey. 100 and 94% of oral dose cleared at two days in mouse and monkey respectively. Rat and dog: triexponential excretion profile with biological half-lives of 0.1, 0.7, and 5.9 days in rat and 0.1, 7.6, and 33.8 days in dog 98 and 90% of oral dose cleared at two days in rat and dog respectively.	Reliability 2-3	Furchner et al. 1968; *This study is evaluated in an addendum to section 6*
Intravenous	mouse/rat /monkey/dog	Silver nitrate	Triexponential excretion profile		

Furchner, J.E, Richmond, C.R. and Drake, G.A. (1968) Evaluated in IIIA 06 Silver Addendum 1 Reliability 2-3			Slower clearance rate compared with clearance after oral administration. Increased difference between species (from 15 in dog to-82% in mouse at 2 days)		
Intraperitoneal Furchner, J.E, Richmond, C.R. and Drake, G.A. (1968) Evaluated in IIIA 06 Silver Addendum 1 Reliability 2-3	mouse/rat /monkey/dog	Silver nitrate	Retention in all tissues resembles whole-body retention except for brain and spleen that seem to retain silver longer.		
Intramuscular Scott, K.G. and Hamilton, J.G. Reliability 2	Rat	Silver nitrate 0.4, 4.0 mg/kg/day	Biliary excretion involved Low dose: ~89% of radioactivity absorbed from the low dose excreted via feces, ~2.2% retention in liver and 4.2% in GI tract. Highest concentrations in % per organ: GI tract followed by liver, blood, kidney, skin, muscle, bone, heart and lungs and spleen. in % per gram: kidney, followed by liver, GI tract, spleen blood, heart and lungs, bone, skin and muscle. High dose:	Reliability 3	Scott and Hamilton 1950 *This study is evaluated in an addendum to section 6*

			~37% of radioactivity absorbed from the high dose excreted via feces, ~34% retention in liver and 8% in GI tract. Highest concentrations in % per organ: liver followed by GI tract, skin, blood, spleen, muscle, bone, kidney, heart and lungs. in % per gram: liver followed by spleen, GI tract, kidney, heart and lungs, skin, blood, bone and muscle.		
Intravenous Scott, K.G. and Hamilton, J.G. Reliability 2	Rat	Silver nitrate 0.4, 4.0 mg/kg/day	~93% of radioactivity absorbed excreted via feces after 4 days. Highest concentrations in % per organ: large intestine followed by blood, muscle ,skin, liver, bone, small intestine, kidney, testes, brain, adrenals, spleen, heart, pancreas, stomach, fat, lungs, eye. in % per gram: adrenals followed by, pancreas, large intestine, kidney, fat spleen, heart, brain, blood, liver, lungs, small intestine,eyes , testes, stomach, skin, bone, muscle.		
Dermal Published research	guinea pig/human		Refers to the ATSDR report (1990) citing Snyder et al., 1975 and Wahlberg et al., 1965	Reliability 3-4	IIIA 6.2(02) Summary by [redacted] (2005)

Oral/iv Published report			The toxicokinetic discussion in the document mainly refers to the results of Furchner et al (see IIIA 6.2-01)	Reliability 3	IIIA 6.2(03) US EPA (1998) Integrated Risk Information System.
Oral Handbook on the Toxicology of Metals.			This document is one of the references included in 6.2(01). Some of the results discussed are therefore already included in this table. Further articles referred to:	Reliability 3	IIIA 6.2(04) Fowler, B.A. and Nordberg, G.F. (1986)
Intraperitoneal	Rat	Silver nitrate	Clearance: Half-lives: 40 hours for clearance from blood, plasma, kidneys and liver. Circa 70 hours for the spleen and 84 hours for the brain.	Original publication not evaluated	Matuk (1983)
Inhalation	Rabbit		30% of deposited silver particles cleared from the lungs within a day and a further 30% in the following week.	Original publication not evaluated	Camner et al (1974)
Inhalation	Dog		Biological clearance half-lives in lungs: 1.7, 8.4 and 40 (accounting for 59, 39 and 2% of administered dose). Biological clearance half-lives in liver: 9 and 40 days (accounting for 97, and 3% of administered dose).	Reliability 2-3	Phalen and Morrow (1973) *This study is evaluated in an addendum to section 6*
Inhalation	Human		Inhaled silver is distributed to the liver. Biological half-lives of 1 and 52 days are assumed to represent rapid lung clearance by ciliary action and liver clearance respectively.	Reliability 3-4	Newton and Holmes (1966) *This study is evaluated in an addendum to section 6*

Oral	Human (single case)	Silver acetate	18% absorption	Original publication not evaluated	East et al. (1980
Subcutaneous	Rat Sprague-Dawley 4 males	Silver zinc zeolite in 1% carboxymethyl cellulose	Peak tissue levels observed 24 hours ≤ 1% and 56.8% excretion via urine and faeces at 7 days Half-life in blood: 61.6 ± 9.4 hours. 2.4% maximum dermal absorption	Reliability 2-3	IIIA 6.2(05) (1992)
Percutaneous		Silver zinc zeolite (10%) cream	Damaged skin: 0.24 and 5.38% excretion in urine and faeces at 7 days. Half-life in blood: 49.5 ± 3.5 hours Normal skin: blood levels too low for analysis 0.12 and 1.1% excretion in urine and faeces at 7 days.		
Oral	Chicken Published research	1 ppm CuSO4x5H2O, 0, 10, 25, 50, 100, 200 ppm Ag2SO4	No specific information on ADME. Results indicate that silver may function as a copper antagonist.	Reliability 3	IIIA 6.2(06) Hill, C.H., Starcher, B. and Matrone, G. (1964)
In vitro	Rat hepatocytes Published research	Silver nitrate silver lactate (10-70 µM final concentration of Ag+)	No specific information on ADME. Results show a decrease in intracellular thiols and lipid peroxidation, in treated hepatocytes. It is postulated that this may lead to the depletion of the intracellular GSH pool and thus be involved in silver cytotoxicity.	Reliability 3	IIIA 6.2(07) Baldi, C., Minoia, C., Di Nucci, A., Capodaglio, E. ad Manzo, L. (1988)
	Published report from ATSDR		This document serves as one of the main references to the summary in		IIIA

			6.2(01). The articles referred to in this document are already included in this table.		6.2(08) Agency for Toxic Substances and Disease Registry (ATSDR). (1990)
	Published report prepared for the Oak Ridge Reservation Environmental Restoration Program		This document is partly based on the ATSDR report. The results discussed are thus already included in this table. Further articles referred to:	Reliability 3	IIIA 6.2(09) Faust, R. (1992)
Intratracheal instillation	Dog	Metallic silver Each anaesthetised dog inhaled 10-20L of aerosol tagged with silver-110m via tracheal intubation during a 7-15 minute exposure period	96.9 % deposited in lungs, 2.4% in liver and 0.35% in blood after six hours with remaining silver detected in gall bladder and bile, intestines and stomach. The distribution in tissue type (if not considering silver in the lung) remained similar after 225 days with most silver found in liver (77%).	Original publication not evaluated	*Phalen and Morrow (1976)*
Oral	Rat	Silver nitrate and silver chloride	Wide distribution with high concentrations found in the reticuloendothelial tissues.		Olcott (1948) *This study is evaluated in an addendum to section 6*
In vitro skin absorption	Human (full thickness female abdominal skin)	1% JMAC Cream R10	Dermal absorption is <0.31% Dermal absorption of this formulation is not considered relevant for the risk assessment of the silver containing active substance.	Reliability 2	IIIA 6.2(10) Walters, K.A. and James, V.J. (1994)
Intraperitoneal Percutaneous	Guinea Pig Published research	Silver nitrate, 0.239M (along with 7 other metal compounds)	Dermal absorption was not investigated in the study. The absorption rate reported (< 1% per five hour period) was determined in a previous in vivo study.	Reliability 4	IIIA 6.2(11) Wahlberg, J.E. (1965)

Percutaneous	Guinea Pig Published research	Silver nitrate, (along with 5 other metal compounds) 0.00048, 0.005, 0.08, 0.118, 0.239, 0.398, 0.753, 4.87M	Dermal absorption less than 4% based on the disappearance of radioactive compound from the cutaneous surface of the living guinea pig	Reliability 3-4	Skog, E, Wahlberg, J.E. (1963) This study is evaluated in an addendum to section 6

3.1.1 Short summary of the toxicokinetic information

There is no substance-specific data on silver zeolite available.
However, it is assumed that the active substance dissociates during acidic conditions (published information by Fruijtier-Pölloth 2009, discussed in silver zinc zeolite CAR) and the silver in silver zeolite is absorbed following release in the gastrointestinal tract. Therefore, the toxicokinetics of the silver part of the active substance may be estimated from data obtained for a different SCAS. In case silver would be absorbed also in the form of the parent compound, it would still be more conservative to only consider the absorption of silver ions when deriving the AEL.
Consequently, the oral absorption of silver ions is assumed to be applicable also to silver zeolite.
The active substance/product is used solely for treatment of articles thus only industrial workers will be exposed to the active substance whereas consumers will be exposed to silver ions released from the articles. Therefore, information on dermal absorption of the silver ion is considered more relevant for risk assessment.
Description of data on silver: The data available and considered to be of relevance for understanding the silver ion toxicokinetics is briefly summarised below. The data from open literature include summary reports prepared by the consultant company engaged by the Silver Task Force, by the United States Environmental Protection Agency (US EPA), the Agency for Toxic Substances and Disease Registry (ATSDR) and the Oak Ridge Reservation Environmental Restoration Program. In addition, Doc IIIA also includes a textbook chapter on silver toxicity, an in vitro mechanistic study and two studies on percutaneous absorption.
Despite a number of summaries, the amount of information is still limited since some of the documents (e.g. 6.2(01) and 6.2(09)) are principally based on the summary report prepared by the ATSDR (6.2(08)). The reviews summarises case reports and published research performed with silver nitrate/lactate or metallic silver.
The information is rather old and the majority of studies are poorly reported but the most robust data for silver nitrate indicate an oral absorption of 5% in mammals (discussed below).
Silver nitrate is a highly soluble substance and thus expected to be completely dissolved in the gastro-intestinal tract before absorption. Therefore, this information is considered relevant for the toxicokinetics of silver ions released from silver zeolite. Due to the excess of chloride ions in the stomach, it seems reasonable to assume that silver ions released from SCAS will rapidly form silver chloride.
Oral absorption/Excretion: according to published summaries, the general understanding is that only a small amount of silver (<10 %) is absorbed by mammals following oral administration. This figure is mainly based on data from a study by Furchner et al which is summarised in an addendum to Doc IIIA, section 6. This study investigated the excretion of silver in mice, rats, dogs and monkeys following oral or intravenous administration of silver nitrate. The research by Furchner et al shows a biexponentional excretion profile in mice and monkeys upon oral administration whereas a triexponential excretion profile is observed in dogs and rats. Since only dogs were assayed for a sufficiently long period, it was assumed that the long component would have been detected if excretion had been assayed longer also in the other species. The two-day clearance via urine and faeces ranged between 90 % and 99 % in the different species following oral administration and between 15 and 82 % following an intravenous dose. Only a minor fraction was excreted in urine. The interspecies difference in clearance rate was explained to as the differences in time taken for passage through the gut.
This study was not performed according to any guideline or GLP and there was no detailed information on the test substance (with respect to purity and other physical data), test animals (housing and feeding conditions) and residues in bile, tissues and carcass were not

measured. However, the strength of the study is that results are based on a large data set including four different species and between 4 and 28 animals in each experiment.
Based on the cumulative whole-body excretion in mouse, rat, monkey and dogs of 99.6%, 98.3%, 94.4 and 90.4% respectively following an oral dose, the oral absorption of silver ions and consequently of silver zeolite in mammals is estimated at 5 %. This figure is expected to be conservative since the excretion data may include residues that were absorbed and then excreted in bile. Moreover, the absorption could also be higher if silver is absorbed also in the form of the parent.

Distribution/excretion: According to information available in the open literature, the silver absorbed from silver nitrate undergoes a first-pass effect in the liver and is excreted into bile after being conjugated to gluthathione. The biliary excretion appears to vary between species and the mechanism seems to be saturated at higher doses, at least in the rat (Scott and Hamilton 1950).
The silver absorbed from silver nitrate appears to be widely distributed in the rat. Following an intramuscular dose of silver nitrate the highest amounts of silver were found in the GI tract followed by liver, blood, kidney, skin, muscle, bone, heart, lungs and spleen (Scott and Hamilton, in addendum to the toxicological section of Doc IIIA). Microscopic analyses of tissues from rats orally exposed to silver nitrate and silver chloride in sodium thiosulphate is presented in a publication by Olcott (1948). Silver was regularly found in histiocytes of lymph nodes and liver, in association with the reticulum fibrils of the sinuses of the lymph nodes and the periphery of the malpihian bodies of the spleen and in close approximation to blood vessels (between endothelium and epithelium of thyroid, choroid of the brain and the glomeruli and tubules of the kidney) It was also found near or in fine blood vessels of pancreas, adrenal medulla, pituitary body (in pars nervosa), choroid of the eye and in striated muscle. According to Olcott (1948), a few black granules were observed in the bone marrow but it was not possible to determine whether or not this was silver and the bone marrow of rats exposed to either silver or water appeared the same. Consequently, it is not possible to conclude whether or not the substance is distributed to the bone marrow.
Accumulation: Silver accumulates in tissues and organs. Visible deposition of silver in human skin is a codition known as argyria and is further discussed in sections 3.6 and 3.11.
Dermal absorption: There is no robust information available. In the absence of substance-specific data it is not possible to set an exact figure for dermal absorption. Nevertheless, the substance is an ion exchanger and it is assumed that at least some dermal absorption will be in the form of ions released from the active substance. In literature, a dermal absorption of 1% is commonly reported. This figure is also used by the applicant and is based on a study by E. Skog and J.E Wahlberg (1963) in which the uptake of silver nitrate through intact skin of guinea pigs was studied.
This study is relatively old and was not performed according to any guideline or principles of GLP. Moreover, the methodology used and the results obtained were poorly reported (the study is summarised in the document denoted IIIA 06_Silver Addendum 1 – Additional toxicological information).
The dermal absorption was determined as the amount of radioactivity that disappeared from a treated area on living guinea pigs during five hours. For the majority of animals, the dermal absorption was below 1 % but the dermal absorption in one animal was in the range 3.0-3.9. Due to all uncertainties in the study, it is considered appropriate to conclude a dermal absorption based on the upper-range value (i.e. 4 %) in order to cover all animals in the study. This value is expected to be conservative because it is based on the assumption that all radioactivity that disappeared from the test area entered the systemic circulation through the skin.
Therefore, the results from this study is considered to support a refinement of the default value of 100% to 5% and consequently to assume that 5% of silver ions released from silver zeolite is absorbed through the skin.

This value is supported also by the general conception that oral absorption rarely exceeds dermal absorption[11].
It should be noted that dermal exposure to the active substance is only expected during industrial uses where the user is expected to wear PPE. Consumers are expected to be exposed to ions released form the treated article.

3.1.2 Values and conclusions used for the risk assessment

Value(s) used in the Risk Assessment – Oral absorption	
Value(s)*	5%
Justification for the selected value(s)	Based on the most robust information available for silver nitrate, it is assumed that 5% of silver ions released from AgION Antimicrobial Type LGK is orally absorbed (see 3.1.1). This value is considered applicable to the active substance taking into account that it is assumed to dissociate prior to absorption and that the effects considered for the derivation of the AEL are linked to the silver ion (pigmentation).

* please include the concentration range(s) and type of formulation(s) the values are applicable for, if relevant

Value(s) used in the Risk Assessment – Dermal absorption	
Value(s)*, **	5% (active substance and silver ions released from treated articles)
Justification for the selected value(s)	Despite the lack of robust data, it is assumed that 5% of silver ions released from AgION Antimicrobial Type LGK is absorbed through the skin (see 3.1.1).

* estimated to be applicable to all concentration range(s) of the active substance
** the dermal absorption value is applicable for the active substance and might not be usable in product authorization

Value(s) used in the Risk Assessment – Inhalatory absorption	
Value(s)*	100%
Justification for the selected value(s)	Deafult value (no data available)

* please include the concentration range(s) and type of formulation(s) the values are applicable for, if relevant

Conclusion(s) used in the Risk Assessment – Distribution	
Conclusion	The form(s) of silver absorbed is assumed to be widely distributed however there is no clear evidence that silver is distributed to the bone marrow.
Justification for the conclusion	The conclusion is based on published research performed with silver nitrate.

11 Discussed in Guidance Notes On Dermal Absorption, Series on Testing and Assessment, No. 156

Conclusion(s) used in the Risk Assessment – Metabolism	
Conclusion	According to information available in the open literature, the silver absorbed from silver nitrate undergoes a first-pass effect in the liver and is excreted into bile after being conjugated to gluthathione. The biliary excretion appears to vary between species and the mechanism seems to be saturated at higher doses, at least in the rat.
Justification for the conclusion	The conclusion is based on published research performed with silver nitrate.

Conclusion(s) used in Risk Assessment – Elimination	
Conclusion	More than 90% of administered dose of silver nitrate is excreted within 2 days, almost exclusively in feces. Silver can accumulate in organs and tissues.
Justification for the conclusion	Conclusion is based on published research performed with silver nitrate administered to mice, rats, dogs and monkeys.

Data waiving	
Information requirement	None
Justification	Despite lack of substance-specific data on AgION Antimicrobial Type LGK and robust data on silver ions, further testing is not considered justified as sufficient data is available to establish a toxicological profile of the substance and perform a (conservative) risk assessment.

3.2 ACUTE TOXICITY

3.2.1 Acute oral toxicity

Summary table of animal studies on acute oral toxicity						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance Dose levels, Type of administration** *(gavage, in diet, other)*	**Signs of toxicity** *(nature, onset, duration, severity, reversibility)*	**Value LD_{50}**	**Remarks** *(e.g. major deviations)*	**Reference (in core dossier)**
Oral OPPTS 870.1100 OECD TG 425 GLP Reliability: 1	Albino rat Sprague-Dawley CD 3 females	AgION Antimicrobial Type AD 5000 mg/kg bw Single dose 14 day observation period	Stains and diarrhoea	>5000 mg/kg bw	Only three test animals.	IIIA 6.1.1(07)

Summary table of human data on acute oral toxicity				
Type of data/ report Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in the Risk Assessment – Acute oral toxicity	
Value	LD_{50} >5000 mg/kg
Justification for the selected value	Value set based on results from a study in rat.

3.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

The acute oral toxicity of the type of silver zeolite considered in this review, Agion Antimicrobial Type LGK, is represented by data obtained with Agion Antimicrobial Type AD which was tested in a GLP-compliant study in rats (read across is discussed in a confidential document).
All animals survived a single dose of 5000 mg Type AD/kg bw and there were no clinical signs observed in the study. It is noted that less animals than recommended in OECD TG 401 were used. However, the result is clear and this deviation is not considered to invalidate the study. than The LD50 is thus above 5000 mg/kg bw.

3.2.1.2 Comparison with the CLP criteria

The criteria reads:
"Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in Table 3.1.1. Acute toxicity values are expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values or as acute toxicity estimates (ATE).
Category 1: ATE≤ 5
Category 2: 5 < ATE≤50
Category 3: 50 < ATE≤ 300
Category 4: 300 < ATE ≤ 2 000"
The LD50 is thus above 5000 mg/kg bw and thus above the range for classification.

3.2.1.3 Conclusion on classification and labelling for acute oral toxicity

There is no human data available but the LD 50 observed in the rat study is above 5000 mg/kg bw indicating that AgION Antimicrobial Type AD, and hence also Type LGK, does not fulfil criteria for classification.

3.2.2 Acute dermal toxicity

Summary table of animal studies on acute dermal toxicity					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance, Vehicle, Dose levels, Surface area,**	**Value LD_{50}**	**Remarks** *(e.g. major deviations)*	**Reference**
OPPTS 870.1200 In compliance with OECD TG 402 GLP Reliability: 1	Albino rat Sprague-Dawley 5/sex	AgION Antimicrobial Type AD 24 hour exposure 14 day observation period	5000 mg/kg bw	None	IIIA 6.1.2-08

Summary table of human data on acute dermal toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in the Risk Assessment – Acute dermal toxicity	
Value	LD_{50} >5000 mg/kg
Justification for the selected value	The value is set based on the results from study in rat.

3.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

The acute dermal toxicity of the type of silver zeolite considered in this review, AgION Antimicrobial Type LGK, is represented by data on AgION Antimicrobial Type AD obtained in a GLP-compliant study in rabbits.
All animals survived a single dose of 5000 mg/kg bw and there were no clinical signs or skin effects observed.

3.2.2.2 Comparison with the CLP criteria

The criteria reads:
"Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in Table 3.1.1. Acute toxicity values are expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values or as acute toxicity estimates (ATE).
Category 1: ATE≤ 5
Category 2: 5 < ATE≤50
Category 3: 50 < ATE≤ 300
Category 4: 300 < ATE ≤ 2 000"
The LD 50 value was > 2000 mg/kg bw and thus outside of the ATE range for classification.

3.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

There is no human data but the LD 50 observed in the rat study is above 5000 mg/kg bw indicating that AgION Antimicrobial Type AD and hence also LGK do not meet criteria for classification with respect to acute dermal toxicity.

3.2.3 Acute inhalation toxicity

Summary table of animal studies on acute inhalation toxicity					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance, form** *(gas, vapour, dust, mist)* **and particle size** *(MMAD)* **Actual and nominal concentration, Type of administration** *(nose only / whole body/ head only)*	**Value LC_{50}**	**Remarks** *(e.g. major deviations)*	**Reference**
Inhalation whole body OECD TG 403 GLP Reliability:2	Albino rat Sprague-Dawley 5/sex	AgION Antimicrobial Type AD 2.05 mg/L 4 hours 14 day observation period	>2.05 mg/L Red ocular discharge	Unclear if 2.05 mg/L represents the maximum attainable concentration	IIIA 6.1.3-05

Summary table of human data on acute inhalation toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in the Risk Assessment – Acute inhalation toxicity	
Value	LC_{50}>2.05 mg/L (presumed to be the highest attainable concentration)
Justification for the selected value	The value is set based on results from a robust animal study.

3.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The acute inhalation toxicity of the type of silver zeolite considered in this review, AgION Antimicrobial Type LGK, is represented by data obtained in a whole-body exposure study with AgION Antimicrobial Type AD.
It is not clear from the original report whether 2.05 mg/L represents the maximum attainable concentration or if it is the highest dose tested. The study was conducted according to US EPA OPPTS 870.1300, a guideline in which 2 mg/L is considered to be a limit dose and no further testing is needed unless there are mortalities at this level. The limit dose for acute inhalation toxicity studies is discussed in the current OECD TG 403 and in a draft report of the expert consultation meeting on acute inhalation toxicity. The document states that it may be technically challenging to achieve both a concentration of 5 mg/L and particles of respirable size.
Since there were no deaths at 2.05 mg/L, the particle size was in the respirable range (mass median aerodynamic diameter value of 3.3 µm±1.9) and a concentration of 2 mg/L seems to be an acceptable limit dose in a recognised guideline, the result obtained with Type AD is considered acceptable.

3.2.3.2 Comparison with the CLP criteria

The criteria reads:
"Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in Table 3.1.1. Acute toxicity values are expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values or as acute toxicity estimates (ATE)."
The acute inhalation toxicity categories and acute toxicity estimates (ATE) of each category for dusts and mists (mg/l):
Category 1: ATE≤ 0.05
Category 2: 0.05 < ATE≤0.5
Category 3: 0.5< ATE≤ 1.0
Category 4: 1.0 < ATE ≤ 5.0"

3.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

There is no human data available but the LC 50 observed in the rat study is above 2.05 mg/l indicating that Type AD and hence also Type LGK does not fulfil criteria for classification with respect to acute toxicity via inhalation.

3.2.4 Overall conclusion on acute toxicity

Value used in the Risk Assessment – Acute systemic toxicity	
Value	The LD50 set for acute systemic effects via oral and dermal routes are above 5000 mg/kg. The LC50 value set for systemic toxicity via inhalation is above 2.05 mg/l.

Justification for the selected value	The conclusion is supported by results from animal data performed with AgION Antimicrobial Type AD. Read across between Type AD and Type LGK is considered justified (see confidential document).
Classification according to CLP and DSD	AgION Antimicrobial Type AD does not fulfil criteria for classification hence Type LGK is not expected to fulfil criteria.

Value/conclusion used in the Risk Assessment – Acute local effects	
Value/conclusion	NA
Justification for the selected value/conclusion	Considering that no local effects were observed in the acute toxicity studies performed with AgION Antimicrobial Type AD, Type LGK is not considered to induce local toxicity.

3.3 IRRITATION AND CORROSION

3.3.1 Skin corrosion and irritation

Summary table of in vitro studies on skin corrosion/irritation					
Method, Guideline, **GLP status, Reliability**	**Test substance, Doses**	**Relevant information about the study**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No in vitro studies available.					

Summary table of animal studies on skin corrosion/irritation					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance, Vehicle, Dose levels, Duration of exposure**	**Results** *Average score (24, 48, 72 h), observations and time point of onset, reversibility, other adverse local/systemic effects, histopathological findings*	**Remarks** *(e.g. major deviations)*	**Reference**
OECD TG 404 GLP USA EPA 870.2500 Reliability 1	Rabbit New Zealand White 3 males	AgION Antimicrobial Type AD 0.5 g 4 hour exposure observations at 30-60 min, 24h, 48h, 72h, after patch removal	No effects observed		IIIA 6.1.4-15 (2006d)

Summary table of human data on skin corrosion/irritation				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in the Risk Assessment – Skin irritation and corrosivity	
Value/conclusion	AgION Antimicrobial Type AD is not a skin irritant hence Type LGK is not expected to meet criteria for irritation.
Justification for the value/conclusion	The conclusion is based on the results from a study in rabbits.

3.3.1.1 Short summary and overall relevance of the provided information on skin irritation

Silver Zeolite was applied to the intact skin of the dorsal trunk of three male rabbits under a semi-occlusive gauze patch. After four hours, the patch was removed and the test site was assessed for irritation and /or corrosion after 30-60 minutes and then approximately at 24, 48, and 72 hours after patch removal. All animals appeared healthy and there were no dermal reactions observed.

3.3.1.2 Comparison with the CLP criteria

The CLP states
"On the basis of the results of animal testing a substance is classified as corrosive, as shown in Table 3.2.1. A corrosive substance is a substance that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 tested animal after exposure up to a 4 hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histo-pathology shall be considered to discern questionable lesions."
"Three subcategories are provided within the corrosive category:
subcategory 1A —where responses are noted following up to 3 minutes exposure and up to 1 hour observation;
subcategory 1B — where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and
subcategory 1C — where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days."

There were no reactions observed in the study with silver zeolite AgION Antimicrobial Type AD thus criteria for classification are not fulfilled.

3.3.1.3 Conclusion on classification and labelling for skin corrosion/irritation

There is no human data available but the lack of dermal reactions in the rabbit study indicates that AgION Antimicrobial Type AD and Type LGK do not have skin corrosion/irritation properties fulfilling criteria for classification.

3.3.2 Eye irritation

<table>
<tr><th colspan="6">Summary table of animal studies on serious eye damage and eye irritation</th></tr>
<tr><th>Method, Guideline, GLP status, Reliability</th><th>Species, Strain, Sex, No/group</th><th>Test substance
Dose levels, Duration of exposure</th><th>Results
Average score (24, 48, 72 h), observations and time point of onset, reversibility</th><th>Remarks
(e.g. major deviations)</th><th>Reference</th></tr>
<tr><td>Eye
OECD TG 405
GLP
Reliability 1</td><td>Rabbit
New Zealand White
3 males</td><td>AgION Antimicrobial Type AD
0.06g
Observations at 1h, 24h, 48h, 72h after instillation</td><td>1h, 24h, 48h: Opacity, irititis, conjunctivitis
Mean values at 24, 48 and 72 hours
<table>
<tr><td></td><td>cornea</td><td>iris</td><td colspan="3">conjunctiva</td></tr>
<tr><td></td><td>mean</td><td>mean</td><td>redness</td><td>chemosis</td><td>discharge</td></tr>
<tr><td>1 M</td><td>0.67 (1,1,0)</td><td>0.67 (1,1,0)</td><td>1.67 (3,2,0)</td><td>1.33 (2,2,0)</td><td>1.0 (2,1,0)</td></tr>
<tr><td>2 M</td><td>0.67 (1,1,0)</td><td>0.67 (1,1,0)</td><td>1.67 (3,2,0)</td><td>0.67 (1,1,0)</td><td>0.33 (1,0,0)</td></tr>
<tr><td>3 M</td><td>0 (0,0,0)</td><td>0.33 (1,0,0)</td><td>1.0 (2,1,0)</td><td>0.33 (1,0,0)</td><td>0.33 (1,0,0)</td></tr>
</table></td><td>Classification not required</td><td>IIIA
6.1.4-16</td></tr>
</table>

Summary table of human data on serious eye damage and eye irritation				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in Risk Assessment – Eye irritation and corrosivity	
Value/conclusion	AgION Antimicrobial Type LGK is not expected to meet criteria for eye irritation.
Justification for the value/conclusion	Results from a study in rabbits indicate that AgION Antimicrobial Type AD causes eye reactions but the mean scores do not fulfil criteria for eye irritation.

3.3.2.1 Short summary and overall relevance of the provided information on eye irritation

The eye irritation potential of AgION Antimicrobial Type LGK is represented by data on AgION Antimicrobial Type AD. Type AD was instilled into the eyes of male rabbits and caused initial irritation that was resolved by the 72 hour reading.

3.3.2.2 Comparison with the CLP criteria

The criteria for classification in category 1 (irreversible effects on the eye) reads:
"If, when applied to the eye of an animal, a substance produces:
– at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
– at least in 2 of 3 tested animals, a positive response of:
– corneal opacity ≥ 3 and/or
– iritis > 1,5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material."

The criteria for classification in category 2 (irritating to eyes) reads:
"if, when applied to the eye of an animal, a substance produces:
— at least in 2 of 3 tested animals, a positive response of:
— corneal opacity ≥ 1 and/or
— iritis ≥ 1, and/or
— conjunctival redness ≥ 2 and/or
— conjunctival oedema (chemosis) ≥ 2
— calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days"

The effects noted do not fulfil the criteria for classification but it is noted that the individual scores for conjunctival redness (1.7) in 2/3 rabbits are only slightly below the cut-off (2) for classification as Eye irrit. 2 in Regulation EC 1272/2008.

3.3.2.3 Conclusion on classification and labelling for eye irritation

There is no human data available but the lack of significant reactions in the rabbit study indicates that AgION Type AD does not fulfil criteria for classification.

3.3.3 Respiratory tract irritation

Summary table of animal studies on respiratory tract irritation					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance** **Dose levels, Duration of exposure**	**Results** *clinical signs, histopathology, reversibility*	**Remarks** *(e.g. major deviations)*	**Reference**
No data available					

Summary table of human data on respiratory tract irritation				
Type of data/report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in the Risk Assessment – Respiratory tract irritation	
Conclusion	AgION Antimicrobial Type LGK is not expected to cause respiratory tract irritation.
Justification for the conclusion	There is no robust data on respiratory effects following repeated exposure via inhalation. However, in the absence of histopathological findings indicative of upper respiratory irritation in the acute inhalation study, the concern for respiratory irritation is low.

3.3.4 Overall conclusion on corrosion and irritation

Conclusion used in the Risk Assessment – Corrosion and irritation	
Value	AgION Antimicrobial Type AD is irritating to eyes but the severity grade does not meet criteria for classification. Consequently AgION Antimicrobial Type LGK is not expected to meet criteria for classification for skin and/or eye irritation.
Justification for the selected value	The conclusion is based on results from animal data (rabbit).

Classification according to CLP and DSD	The effects observed do not fulfil criteria for classification.

3.4 SENSITISATION

3.4.1 Skin sensitisation

Summary table of animal studies on skin sensitisation					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance, Vehicle,** **Dose levels, Route of exposure** *(topical/intradermal, if relevant)*, **Duration of exposure**	**Results** *(EC3-value or amount of sensitised animals at induction dose)*	**Remarks** *(e.g. major deviations)*	**Reference**
Buehler US EPA 870.2600 Reliability 2	Guinea pigs 20 males 5 naïve control males	Antimicrobial Type AD Induction: 55% w/w test solution in distilled water Challenge: 41%w/w test solution in distilled water Induction: 6 hours (1/week) x 3 Challenge: 27 days post first application Evaluation 24 and 75 hours post challenge	The frequency of reactions graded 0.5 was higher after challenge than after the intradermal injections. The frequency observed 24 hours after challenge was 15% higher than in naïve controls. Based on these results, Antimicrobial Type AD is considered to have sensitizing properties.	A score of 0.5 is not counted as a positive response according to the criteria in study report.	IIIA 6.1.5-08
LLNA OECD 429 (2010) US EPA OPPTS 870.2600 (2003) Reliability 1	CBA/J mice 5 female/dose 3 controls	Antimicrobial Type LGK 5%, 10% and 25% suspended in propylene glycol	No skin sensitisation potential at doses up to 25% w/w	The top dose of 25% w/w is stated to be the highest soluble concentration.	IIIA 6.1.5-01 (Doc IIIA silver zeolite, separate document)

Summary table of human data on skin sensitisation				
Type of data/report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data avialable				

Conclusion used in Risk Assessment – Skin sensitisation	
Value/conclusion	According to the results from the study performed with AgION Antimicrobial Type LGK, this type of silver zeolite does not cause skin sensitisation.
Justification for the value/conclusion	The conclusion is based on results from a LLNA test.

3.4.1.1 Short summary and overall relevance of the provided information on skin sensitisation

The skin sensitisation potential of the type of silver zeolite considered in this review, Agion Antimicrobial Type LGK, was tested in a local lymph node assay. The test material was applied in propylene glycol at concentrations of 0% (vehicle control), 5%, 10% and 25% to the ears of five female CBA/L mice per concentration during three consecutive days. A positive control group of five mice was similarly treated with 25% α-hexylcinnamaldehyde (HCA). At sacrifice, the draining (auricular) lymph nodes were removed, the lymphocytes harvested and the radioactivity measured by liquid scintillation counting. Based on the analysis of radioactivity, stimulation indices (SI) for the groups of mice treated with 5%, 10% and 25% test material were calculated to be 1.04, 0.91 and 1.62 respectively. According to OECD TG 420, a stimulation index of 3 or higher is considered a positive result.
Since the SI values were below 3, Agion Antimicrobial Type LGK is not considered to have a skin sensitisation potential at doses up to 25%.
However, since the top dose of 25% did not induce any signs of systemic toxicity or skin reactions, it may be questioned whether or not this result could be considered representative of the neat active substance. The study report states that testing of higher concentrations was limited by the low solubility of the substance. Taking this into account as well as an estimated low dermal absorption rate of 5%, it may be argued that there is an intrinsic barrier preventing skin sentisizing reactions.

The skin sensitisation potential of the type of silver zeolite used to represent AgION in the assessment of acute toxicity endpoints and irritation, i.e. Antimicrobial Type AD, was tested in a Buehler test.
Treatment with AgION Antimicrobial Type AD in guinea pigs resulted in a skin response scored 0.5 in 7/20 (35%) of animals compared to 2/10 (20%) in naïve controls (no sham control was included)) after 24 hours. A second reading was made at 75 hours instead of at 48 hours.
A positive response in 15% of animals is normally considered as a positive response in a Buehler test but as score 0.5 was not counted as a positive response by the study author, the substance was not regarded as a sensitizer in the study.

The scoring system used by the laboratory differs from the scoring system in OECD TG 406 which does not include a score of 0.5. However, score 0.5 which was defined as "very faint erythema, usually non-confluent" in the study report seems comparable to score 1 (i.e. discrete or patchy erythema) in the scoring system used for GPMT in OECD TG 406. Irrespective of the grade, it can be concluded that a reaction occurred at a higher frequency in treated animals following challenge. The frequency of skin reactions of this type after challenge were thus higher at a test substance concentration of 41% (7/20 test animals) compared to the frequencies observed in test animals after first, second and third inductions with 55% test substance (4/20, 0/20 and 3/20 animals). Therefore, the higher frequency following application of a lower dose is considered to indicate a sensitization reaction rather than an irritation effect.
The applicant argues that the skin reactions observed were due to minor skin abrasion during the clipping process and handling of the animals. This is not supported from the study report and if this would be the case, a similar frequency would be expected for treated and untreated animals and the reaction would not be expected to last until 24 hours post challenge. Another argument put forward is that the skin reactions observed represent reactions to the bandage (despite best practice use of hypoallergenic dressings) as it is common for guinea pigs to react to periods of wearing occlusive dressings by developing a slightly reddened skin which typically resolves over the following 24 hours. Again, if this was the sole explanation, the frequency of reactions could be expected to be similar between treated and untreated animals.
Therefore, in contrast to the study author, it is not considered safe to exclude that this type of silver zeolite has sensitizing properties.

A similar result was obtained in a different Buehler test performed with a 75% w/w silver citrate solution (Doc IIIA, 6.1.5-02). In similarity with the Type AD study, reactions graded 0.5 were observed in more than 15% of treated animals (80 and 70% of animals at 24 and 48 hours respectively compared to 60 and 50% in control animals). This was also disregarded by the study author.
For elemental silver and silver nitrate, information available in the IUCLID Chemical Data Sheet posted on the website for the European chemical Substances Information System (ESIS) states that mild allergenic responses observed have been attributed to 20 years exposure to silver in dental amalgams. This case report is also described in the report prepared by the Agency for Toxic Substances and Disease Registry (Doc IIIA, section 6.2(09)). According to the ATSDR report, mild allergenic responses have also been observed in a worker dermally exposed to powdered silver cyanide (6 months of exposure) and a worker in contact with radiographic processing solutions (exposure 10 years). Two cases of skin sensitisation following burn treatment with silver sulfadiazine cream have been reported (USEPA 1980).
The applicant argues that other components of amalgam are responsible for the sensitization reactions observed and refers to an article by McCullough, M.J. and Tyas, M.J (2008). These authors state "The allergens thought to be responsible are usually mercury or mercury compounds, and rarely tin, zinc, copper, silver, gold or palladium." but there are no references given to support the statement. Sensitisation reactions following therapeutic uses of silver nitrate, colloidal silver or silversulfadiazine are described in a textbook by A.B. G Lansdown . The book also states that allergic reactions were observed in patch tests with 5 or 10% solutions of silver nitrate when patients were exposed to "aged" (i.e. more ionised) solutions but not to freshly prepared solutions.
Due to the limited information available human cases, it is difficult to conclude if this data is reliable and/or relevant for the assessment of silver zeolite.

Even if silver ions may have an intrinsic ability to cause sensitisation, the negative results obtained with other SCAS indicate either a low potency of the silver ion or that the sensitising potential of a SCAS depend on the amount of silver ions released. Considering that a 44% solution with Type AD containing a higher amount of silver (see confidential document) resulted in a borderline response and a 25% solution with Type LGK containing 5% silver gave no response, it seems realistic to assume that Type LGK neat would not elicit a positive response.

3.4.1.2 Comparison with the CLP criteria

According to the guidance document on the Application of CLP Criteria, test results from the LLNA, GPMT and the Buehler assay can be used directly for classification. For the mouse local lymph node assay (LLNA), a significant skin sensitising effect is defined as a stimulation index (SI) of 3 or higher. Since the SI values obtained were all below 3 the criteria for classification are clearly not met on the basis of this result. However, a study performed with a different silver zeolite containing a higher silver content gives some indications of a sensitising potential of silver and further indiactions can also be found in some published case reports. Unfortunately, the information available on the human cases is limited and confidence in data is thus low.

3.4.1.3 Conclusion on classification and labelling for skin sensitisation

Based on the results from a LLNA test performed, Agion Antimicrobial Type LGK does not fulfil criteria for classification. The indications of a sensitising potential of silver ions in a study performed with a different silver zeolite and described in published case reports are not considered sufficient evidence to consider Agion Antimicrobial Type LGK to fulfil criteria for classification.

3.4.2 Respiratory sensitisation

Summary table of animal data on respiratory sensitisation					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance** **Dose levels, Duration of exposure**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available					

Summary table of human data on respiratory sensitisation				
Type of data/report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in the Risk Assessment – Respiratory sensitisation	
Value/conclusion	NA
Justification for the value/conclusion	No data available

3.4.3 Overall conclusion on sensitisation

Conclusion used in the Risk Assessment – Sensitisation	
Value	Data do not indicate a skin sensitising potential of AgION Antimicrobial Type LGK.
Justification for the selected value	The conclusion is based on results from a LLNA test in mice.
Classification according to CLP and DSD	AgION Antimicrobial Type LGK does not fulfil criteria for classification.

3.5 SHORT TERM REPEATED DOSE TOXICITY

3.5.1 Short-term oral toxicity

Summary table of oral short-term animal studies (usually 28-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/group**	**Test substance Dose levels, Route of exposure** *(gavage, in diet, other),* **Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
Two week palatability study Reliability 2	Rat Crl:CDBR VAF Plus	Silver sodium hydrogen zirconium phosphate (AlphaSan RC2000) 250, 500 and 1000 mg/kg bw/day Oral 15 days		No effect on food consumption, body weights or clinical conditions at the top dose.	Read across	IIIA 6.3.1(05) (1994
4 week oral gavage study+ report on histological slides of the gastrointestinal tract Reliability 2	Rat Crl:CD (SD)BR 5/sex	JMAC (14.9% Ag) 300, 750 or 1500 mg kg bw/day /kg bw)	750 (~8 mg silver ion equivalents 1500 (~16 silver ion equivalents /kg bw)	1500 mg/kg bw ↓Bodyweight gain (m, 35%) ↓WBC (f, 30%) ↑AST (m, 158%), ALT (m, >250%*) ↑ALP (m/f, 105/149) ↓Organ weights: thymus (m/f, 47/34**%) Brown discoloration along capillary basement membranes Brown/black particulate material in the lamina propria macrophages discoloration of lymph node sinusoids. Other effects noted: 1500 mg/kg bw ↑RBC (f, 8%), PCV (f, 9%) ↓MCHC (f, 2%) ↑Glucose (f, 52%),	Read across	IIIA 6.3.1(02) IIIA 6.3.1(03) Additional histopathological investigations

Summary table of human data on short-term oral toxicity				
Type of data/report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

The dossier does not contain any information on the short-term toxicity of silver zeolite. The only data available and of relevance for this endpoint is a study performed with silver sodium hydrogen zirconium phosphate and a study with the reaction mass of titanium dioxide and silver chloride.

Assuming no synergism between the different constituents of the substance (i.e. silver and the zeolite), a strategy to fill the data gap could be to estimate the overall short-term NOAEL of Antimicrobial Type LGK from the lowest NOAEL set for the different constituents of the substance, i.e. to calculate the dose of Type LGK needed to achieve the same concentration of the constituent based on content and release:
e.g. estimated NOAEL based on NOAEL for silver ion equivalents:
$NOAEL_{Type\ LGK}$ = lowest $NOAEL_{constituent}$ ÷ ($content_{constituent}$ in Type LGK × % release (Ag release at conditions assumed to mimic conditions in the rat stomach (pH 4, 12 hours)).
Short-term toxicity of silver ion equivalents: There were no effects observed in a two-week palatability study performed with silver sodium hydrogen zirconium phosphate (Alphasan RC 2000) up to a limit dose of 1000 mg/kg bw/d.
JMAC powder, the representative type of reaction mass of titanium dioxide and silver chloride, was tested in a 4 week study in CD rats (6.3.1(02)) and results were further analysed in a follow-up histological examination of the gastrointestinal tract of high dose and control animals (6.3.1(03)).
All rats survived treatment with 300, 750 or 1500 mg JMAC/kg bw/day and there were no remarkable clinical signs.
Effects considered to result from treatment included increased levels of enzymes AST and ALT in high and mid dose animals and increased levels of ALP in all treated groups. The histopathological examinations revealed an increased incidence of abnormal colour and abnormal contents of various organs within the gastro-intestinal tract of high dose animals.

The elevated levels of AST and ALT could not be explained from the histopatological evaluation but a mild toxic injury to the liver was not excluded. However, based on brown discoloration along capillary basement membranes within caecum and the small intestine (ileum), assumed to be silver accumulation, it was speculated that the elevated ALP levels could result from ALP leaking from damaged capillaries. If this would be the case, the increase in ALP observed also in low dose animals would be considered an adverse effect. However, since there were no observations of abnormal colour or abnormal contents in the gastrointestinal tract of low and mid dose animals (which were not included in the follow-up analysis), the increased ALP in isolation considered a sufficient basis for the NOAEL. Therefore, the NOAEL is set at 750 mg/kg bw which, based on silver content and release at pH4 (37°C), corresponds to a dose of 8 mg silver ion equivalents /kg bw/day.

Assuming that all effects are caused by silver ions, a NOAEL for this effect can be estimated at 571 mg/kg bw for AgION Antimicrobial Type LGK.

Short term-toxicity of zeolite: In two separate studies conducted in 1979, sodium aluminium silicate was administered consecutively for 14 days to groups of Fischer-344 rats and B6C3F1 mice at concentrations up to 10% w/w in diet. Based on observations of body weight, food consumption and gross necropsy findings, no marked signs of toxicity were reported (Doc IIIA, Section 6, Addendum - Zeolite A Toxicity). Although it is not possible to assess the original data, the information indicates that high doses of

zeolite are well tolerated by rodents (10% w/w corresponds to an internal dose of approximately to 10 or 20 g/kg bw/d in rats and mice respectively, 100 g/kg food (10 w/w%) × 0.12 or 0.2[12]).

Value used in the Risk Assessment – Short-term oral toxicity	
Value/conclusion	There is no substance-specific data available for AgION Antimicrobial Type LGK. If needed, a short-term NOAEL can be estimated: 571 mg Type LGK/kg bw/d.
Justification for the value/conclusion	See below

Data waiving	
Information requirement	Further data is not considered necessary.
Justification	A short-term NOAEL, if needed, can be estimated by calculating the dose of Type LGK needed to achieve the silver concentration at the NOAEL set for JMAC Composite PG.

3.5.2 Short-term dermal toxicity

Summary table of dermal short-term animal studies (usually 28-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Vehicle Dose levels, Surface area, Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available						

[12] Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579. [32 pp.] doi:10.2903/j.efsa.2012.2579. Available online: www.efsa.europa.eu

Summary table of human data on short-term dermal toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in the Risk Assessment – Short-term dermal toxicity	
Value/conclusion	NA
Justification for the value/conclusion	No data available

Data waiving	
Information requirement	No further information is required.
Justification	According to information from the applicant, the active substance is handled in industrial processes where personnel use personal protective equipment including disposable masks, gloves and overalls as well as protective glasses. The equipment used is designed to limit human exposure thus the dermal exposure of professional users is expected to be low. Non-professional users and consumers are exposed to silver ions released from treated items but no dermal exposure to the active substance is anticipated. Taking also into account the lack of effects in a 90-day repeated dose dermal toxicity study performed with AgION Antimicrobial Type AC (see section 3.6.2), the concern for a different toxicity via the dermal route is low. Consequently further studies are not considered justified.

3.5.3 Short-term inhalation toxicity

Summary table of inhalatory short-term animal studies (usually 28-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, form** *(gas, vapour, dust, mist)* **and particle size** (MMAD)**, Actual and nominal concentration, Type of administration** *(nose only / whole body/ head only),* **Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available						

Summary table of human data on short-term inhalation toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in Risk Assessment – Short-term inhalation toxicity	
Value/conclusion	NA
Justification for the value/conclusion	No data available

Data waiving	
Information requirement	No further data required
Justification	In the absence of inhalation studies, it is not possible to exclude that the NOAEL could be lower following inhalation exposure.

	According to a summary document on zeolite A (represented by CAS no 1344-00-9 and 1318-02-1) prepared by HERA 2004 (summarized by the applicant in Doc IIIA Addendum 2- Zeolite A Toxicity), local effects of dust such as focal nonsuppurative inflammatory responses (bronchioloitis and alveolitis) were observed in monkeys exposed to 1, 6 and 50 mg/m3 for 6 hours, 5 days per week during 6, 12 or 24 months. There was no evidence of progressive pulmonary fibrosis or systemic toxicity in this study or in other studies of lower reliability performed with Wistar rats, guinea pigs or Syrian hamsters. In the absence of the original study, it can only be concluded that local inflammation in the lungs can be expected following inhalation. However, the maximum dose (50 µg/L) was far below the limit dose in OECD TG 413 (5mg/L) and it is thus not possible to exclude that other effects could occur at higher doses. Nevertheless, according to the applicant the actual exposure via inhalation is expected to be very low. Therefore, assuming that industrial workers respect work-place routines and that the process takes place in nearly closed systems, the eCA does not consider requests for further animal testing justified for the purpose of this review.

3.5.4 Overall conclusion on short-term repeated dose toxicity

Value used in the Risk Assessment – Short-term repeated dose systemic toxicity	
Value	There is no substance-specific data available for AgION Antimicrobial Type LGK. However, a short-term NOAEL can be estimated if extrapolating the most conservative NOAEL set for an individual constituent of the substance to the dose of Type LGK needed to achieve this concentration: $NOAEL_{Type\ LGK}$= lowest $NOAEL_{constituent}$ ÷ $content_{constituent}$ in Type LGK × 28% release. Using this approach, a short-term NOAEL of 571 mg/kg bw/d can be estimated based on data obtained with JMAC powder
Justification for the selected value	See section 3.5.1.
Classification according to CLP and DSD	See section 3.6.1.3.

Value/conclusion used in the Risk Assessment – Short-term repeated dose local effects	
Value/conclusion	Not applicable
Justification for the selected value/conclusion	There are no substance-specific studies available. However, there were no local effects observed in the acute studies performed with AgION Antimicrobial Type AD.
Classification according to CLP and DSD	Not applicable (see above)

3.6 SUB-CHRONIC REPEATED DOSE TOXICITY

3.6.1 Sub-chronic oral toxicity

Summary table of oral sub-chronic animal studies (usually 90-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance Dose levels, Route of exposure** *(gavage, in diet, other)*, **Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
Oral 13 weeks EPA FIFRA Guideline 82-1 EPA TSCA 40CFR Part 798 Health Effects Testing Guidelines OECD Method 408 EEC Methods for determination of toxicity Reliability: 1	Rat Crl:CDBR VAF Plus 10/sex	Novaron AG-300 (AlphaSan RC5000) (3.8% Ag) 0, 30, 300 and 1000 mg/kg bw/day 300 mg/kg bw/day (~2.9 mg silver ion equivalents /kg bw) 30 mg/kg bw/day (~0.3 mg silver ion equivalents /kg bw)	**NOAEL:** 30 mg /kg bw/day (~0.3 mg silver ion equivalents /kg bw) **LOAEL:** 300 mg /kg bw/day (~3 mg silver ion equivalents /kg bw)	**1000 mg/kg bw** ↑Discoloration of the pancreas (f, 10/10) ↑Discoloration of the Harderian gland (f, 10/10) ↑ALP (m/f 23/34%) **300 mg/kg bw:** ↑Discoloration of the pancreas (f, 10/10) ↑Discoloration of the Harderian gland (f 8/10) ↑ALP (m, 47%) ***Other effects noted:*** ***1000 mg/kg bw:*** ↑PCV (m, 1.8%) ↑RBC (m, 8.2%) ↓MCV (m, 5%) ↓Platelet counts (f, 14%) ↓Thrombotest time (m, 8%) ↑Total protein (m, 4.4%) ↓Total protein (f, 5%) ↓Albumin (f, 9%) ↓Phosphorous (m, 7%)	Read across	IIIA 6.4.1(04) (1995)

				↑Cholesterol (m/f, 52/47%) ↓Protein(u) (f, 25%) ↑Urine volume (f, 41%) ↓Abs spleen weight (m, 21%) ↑Abs spleen weight (f, 14%) ↓Abs testes weight (l/r, 9/11%), ***1000 mg/kg bw:*** ↓Abs epididymides weight (r, 9%), ↑Rel heart weight (m, 12%) ***300 mg/kg bw:*** ↑PCV (m, 3.6%) ↑RBC (m, 6.8%) ↓MCV (m, 4%) ↓albumin (f, 9%) ↑cholesterol (m, 35%) ↓Spleen (m, 21%), ↑Abs spleen weight (f, 21%) ↓Abs testes weight (l/r, 10%), ***30mg/kg bw:*** ↑PCV (m, 3.6%)		
Oral 13 weeks OPPTS 870.3100 Reliability: 1	Dog, Beagle 4/ sex	AlphaSan RC2000 (10.1% Ag) 0, 200, 400 and 1000/700 mg/kg bw/day 400 mg AlphaSan RC2000 /kg bw/day (~10 mg silver ion equivalents /kg bw) 200 mg AlphaSan RC2000 /kg bw/day (~5 mg silver ion equivalents /kg bw)	**NOAEL:** 200 mg /kg bw/day (~5 mg silver ion equivalents /kg bw) **LOAEL:** 400 mg /kg bw/day (~10 mg silver ion equivalents /kg bw)	**1000/700 mg/kg bw/day:** ↑Death (M, F: 1/4) ↓Body weight* (f, 31%, day 84) ↓Bodyweight gain (-1.6kg overall gain (+2 kg in controls)) ↓Food consumption (f, ~30-70%) ↓activity (m: 1/4, f:2/4) ↑ Pigmentation of intestine, liver and kidneys	Read across	IIIA 6.4.1(05) (2002)

				↑ Renal tubular dilation (m/f: 0/1, controls: (m/f: 0/0)) and necrosis (m/f: 0/2, controls: (m/f: 0/0)) ↑Hepatic inflammation (m/f: 4/3, controls: (m/f: 0/1)) hepatic vacuolation (m/f: 1/2, controls: (m/f: 0/0)) necrosis (m/f: 2/1, controls: (m/f: 0/0)) ↑ALP (m/f, ≤181/307%), ↑AST (m, 14%) ↑ALT (m/f ≤75/259) **400 mg /kg bw/day:** ↑Pigmentation of intestine, liver and kidneys ↑Hepatic inflammation (m/f: 1/2) ***Other effects noted:*** ***1000/700 mg/kg bw/day*** *↑Diarrhoea* *↓Sodium (m, 3%)* *↓Potassium* *(f, 8%)* *↓Phosphorous* *(f, 17%)* *↑Cerebral hemorraghes with thrombosis* *(m/f: 0/1, controls: (m/f: 0/0))* *Bronchointerstitial pneumonia* *(m/f: 0/1, controls: (m/f: 0/0))* *Thymic atrophy (m/f: 3/2, controls: (m/f: 0/0)) lymphoid*		

				depletion (m/f: 0/1, controls: (m/f: 0/0)) ***400 mg/kg bw/day*** *↑Diarrhoea* *↓Sodium (m, 2%)* *200 mg/kg bw/day* *↑Diarrhoea* *↓Sodium (m, 2%)*		
*statistical analysis performed on day s 28, 56 and 84 only.						
Oral 90 days US EPA OPPTS Guideline no. 870.3100. DACO 4.3.1-1 Reliability: 1	Zeomic (stated to be AgION Silver Antimicrobial AK) (4.9% Ag, 13.0% Zn) 0, 1000, 6250, 12500 ppm (approximately 64/78, 398/489 and 916/939 mg/kg bw in males and fe-males)	Rat Sprague-Dawley (Crl:CD (SD)IGS BR) 10/sex	NOAEL: 1000 ppm (~1.3 mg silver ion equivalents /kg bw) LOAEL: 6250 ppm (~8.2 mg silver ion equivalents /kg bw)	2500 ppm: ↓Bodyweight (m, ≤8%) ↑Effects on behaviour/activity ↑Erythrocytes (m,10%) platelets (m, 97%) ↓Hb (m/f, 15/10%), HCT (m/f, 9/7%), MCV (m/f 18/11%),, MCH (m/f, 23/15%), MCHC (m/f, 6/4%) ↑ALP (m/f, 70/143%) ↑Pigmentation of pancreas, thymus, mandibular lymph node ↑Mild hemorrhage, inflamma-tion in the Harderian gland (M) ↑Chronic nephritis (M) ↑Urinary pH (m, 11%)↑	Read across	IIIA 6.4.1 (06) (2001)

				↓Urine volume (m/f, n.s.s) 6250 ppm ↑Effects on behaviour/activity ↑Pigmentation of pancreas, thymus, mandibular lymph node ↑ALP (m/f 44/80%) Other effects noted: 12500 ppm ↑Eosinophils (f, 85%) ↑Cholesterol (m/f, 59/67%) ↑Rel heart weight (m, 11%) ↓Counts of vertical and stereo-typy activity(20-30 min) (F) 6500 ppm ↓MCV, MCH (M) ↑Cholesterol (m/f, 58/39%) 1000 ppm ↑Cholesterol (m, 41%) ↓Counts of horizontal, vertical and stereotypy activity during the first ten minutes in males		
Oral 90 days OECD 409 OPPTS 870.3150 EC Directive 87/302/EEC Reliability: 1	Zeomic AK10D Silver 4.9% Zinc 13.0% 0, 10, 50 and 250 mg/kg/day	Dog Beagle	**NOAEL: 50 mg/kg/day** (~1.0 mg silver ion equivalents /kg bw)	250 mg/kg bw ↑Vomiting, head shaking (m,f) ↓Hemoglobin (m, 20%) ↑Increased severity of cortico-medullary tubular basophilia	Read across	IIIA 6.4.1 (07)

			LOAEL: 250 mg/kg/day (~5.1 mg silver ion equivalents /kg bw)	and lymphoid infiltration, interstitial fibrosis and hyaline/cellular casts ↑Discoloration of the pancreas and gastrointestinal tract Other effects noted: 250 mg/kg bw ↑APTT (f, 15%) ↑Creatinine (m, 17%) ↑Cholesterol (f, 42%) ↑ALP, (f (week 6), 64%), ↑Calcium (f, 3.5%) ↓GLDH (f (week 6), 20%), phospholipids (f, 33%) ↑Urinary volume (f (week 6), 250%) ↓Potassium (63%) ↑Ovaries/uterus enlarged All dose levels: ↑Vomiting		

Summary table of human data on sub-chronic oral toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in Risk Assessment – Sub-chronic oral toxicity	
Value/conclusion	The estimated sub-chronic NOAEL of silver zeolite is 21 mg/kg bw/d.
Justification for the value/conclusion	There is no substance-specific data available for AgION Antimicrobial Type LGK. A NOAEL can be estimated by calculating the dose of Type LGK needed to achieve the silver concentration at the NOAEL set for Alphasan RC 5000.

Data waiving	
Information requirement	No further data is required.
Justification	A NOAEL can be estimated by calculating the dose of Type LGK needed to achieve the silver concentration at the NOAEL set for Alphasan RC 5000.

3.6.1.1 Short summary and overall relevance of the provided information on sub-chronic repeated dose toxicity

The dossier does not contain any substance-specific data on the sub-chronic toxicity of silver zeolite. The applicant considers waiving of substance-specific information justified based on the following arguments *"Based on close structural similarity between silver zeolite and silver zinc zeolite and the comparable rate of silver release from these two substances, the available 90 day data are considered adequate to predict the short term repeat dose oral toxicity arising from silver exposure from silver zeolite."*
As discussed in the previous section, it is considered acceptable to estimate a sub-chronic NOAEL from the NOAELs set for individual constituents of the substance. This approach assumes no synergism between the different constituents and to compensate for this potential uncertainty, the overall short-term NOAEL of Antimicrobial Type LGK is proposed to be determined by the lowest NOAEL set for an individual constituent.

Sub-chronic toxicity of silver ion equivalents: The data available for this endpoint include 90-day studies in rats and dogs performed with silver zinc zeolite and silver sodium hydrogen zirconium phosphate, respectively.

Silver zinc zeolite:

Dogs: All dogs survived doses of 10, 50 and 250 mg AgION Antimicrobial Type AK/kg bw/day.

Clinical signs such as head shaking, salivation and vomiting were observed in dogs administered 250 mg/kg bw and the haematological and clinical chemistry analyses made indicated a decreased level of hemoglobin (20/8%) and an increased levels of cholesterol, phospholipids and ALP. The histopathological examinations made revealed discoloration of the pancreas and gastrointestinal tract and histopathological changes in the kidney (increased severity of corticomedullary tubular basophilia and lymphoid infiltration, interstitial fibrosis and hyaline/cellular casts).

The clinical signs observed in all high dose animals throughout the study period (i.e. occasional salivation, shaking of head and vomiting) were claimed to be related to administration route (capsules) or taste or irritancy rather than to the test substance. Since these types of effects are commonly noted in dogs following capsule administration it seems realistic to assume that they represent an unspecific response to a high local concentration of the active substance. However, vomiting brings an uncertainty regarding the dose actually achieved.

The level of hemoglobin was 20 % lower in high dose males compared to controls. Occasional changes in blood parameters were noted also in high dose females (reduced MCV (3%) and prolonged partial thromboplastin time (10%)) but they were not considered toxicologically significant. The effects on haematological parameters indicative of anemia such as decresed Hb, haematocrit, MCV, MCH, MCHC and increased synthesis of erythrocytes were also noted in the rat study (see below).

According to the study author of the rat study 6.4.1(06), alterations in erythropoietic parameters (haemoglobin, haematocrit, MVC, MCH, MCHC and platelet counts) are suggestive of possible zinc toxicity. Zinc toxicity may include inhibition of heme synthesis and/or acute erythrocytic destruction but it is not possible to exclude a similar effect of silver.

According to the document "Guidance on the application of the CLP criteria", a reduction of 20 % or more in Hb concentration is considered a stand-alone criterion for haemolytic anaemia. However, since the 20% reduction was observed at a dose level of 250 mg/kg bw (10% Hb reduction at 50 mg/kg bw) which is 2.5 times above the guidance values (10<C>100 mg/kg bw) for STOT-RE, category 2, it is not considered necessary to classify silver zinc zeolite for this effect.

Enlarged and discoloured ovaries were observed in 3 of 4 high dose females along with enlarged uterus (microscopically: diestrus epithelium). The finding was disregarded by the study author but due to the lack of similar findings in control animals, the significance of these findings must be considered unclear.

The NOAEL was set at 50 mg/kg bw and based on the silver content and the release at pH4 (37°C), the amount of silver released at this dose level was 1 mg/kg bw/day.

Based on silver content and 28% release of silver ions, a NOAEL of 71 mg/kg bw/d can be estimated for silver zeolite.

Rats: All rats survived treatment with 1000, 6250 and 12500 ppm AgION Antimicrobial Type AK (6.4.1(06)) except for a few single rats in each dose group that died during blood sampling. The bodyweights of high dose males were reduced at 5 of the 14 study weeks but only to an extent of ± 8%. The bodyweight gain was reduced by 10% but this parameter was not statistically analysed. The bodyweights and bodyweight gains of high dose females were not affected.

Administration of 6250 ppm (278/366 mg/kg bw) or higher doses resulted in effects on behaviour/activity (hypersensitivity to touch, vocalization, increased activity, aggressive behaviour), pigmentation of pancreas, thymus, the mandibular lymph node and an increase in cholesterol and alkaline phosphatase (ALP).
Increased levels of erythrocytes (M) and platelets (M) were observed in high dose males and decreased levels of Hemoglobin (Hb) (15/10%), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) were observed in high dose males and females. There were no statistically significant differences between the animals in the neurobehaviour, FOB or motor activity evaluations performed except for an increased touch response in high dose animals and a few minor effects observed in the neurological examinations.
The NOAEL was set at 1000 ppm (64/78 mg/kg bw) and based on silver content and release at pH4 (37°C), this dose corresponds to 1.3 mg silver ion equivalents/kg bw/day. Based on silver content and 28% release of silver ions, a NOAEL of 93 mg/kg bw/d can be estimated for silver zeolite.

Silver sodium hydrogen zirconium phosphate:
Dogs: AlphaSan RC2000 was administered to dogs in gelatin capsules containing doses of 200, 400 and 700/1000 mg/kg bw/day during 90 days.
One male and one female dog administered the highest dose died or were humanely killed prior to termination (on the day of the scheduled sacrifice and on day 42, respectively). Both dogs were emaciated. Autopsy showed enlarged salivary glands, engorged gall bladder, thickened stomach and small intestine in the male dog. Observations in the female dog included pale liver, stomach and intestines, a dark and shrunken spleen, a discolored area and dark gel on the occipital region of the brain. Both dogs had discolored contents in the intestinal tract but in the absence of histopathological changes, the study author did not consider the findings to be of toxicological significance. It is noted that similar observations were made in a four week rat study performed with a different SCAS, i.e. the reaction mass of titanium dioxide and silver chloride (JMAC powder) at a dose of 750 mg/kg bw/d. In this study the brown discoloration observed along capillary basement membranes within caecum and the small intestine (ileum) was assumed to be silver accumulation (see core dossier).
The food consumption was reduced in high dose animals during the entire study period and was most pronounced in females (by approximately 30-70%). One high dose male and two high dose females, including the female sacrificed on day 42, stopped eating and had to be force-fed and/or fed moist food to stimulate the appetite. Due to the reduced food consumption, the highest dose was reduced to 700 mg/kg bw on day 43 for females and day 71 for males.
Bodyweights were reduced in females and males from approximately days 14 and 49 respectively and throughout the study. Despite that the mean starting and mean final weights were the same in high dose males (compared to a weight gain of 2.7 kg in controls) and that the mean final weight of high dose females was 1.6 kg less than the mean weight at start (mean weight gain in controls was 4 kg), statistical significance was only achieved at one of the readings. Due to the few number of animals in each group, the non-statistical significant effects on bodyweight gain are yet considered toxicologically significant.
The pathological examinations revealed pigmentation of intestine, liver, kidneys and hepatic inflammation in animals treated with 400 or 1000/700 mg/kg bw/day mg/kg bw. In animals treated with 1000/700 mg/kg bw/day, the hepatic inflammation was accompanied with hepatic vaculolisation and necrosis, increased level of alkaline phosphatase (ALP), aspartate transaminase (AST) and

alanine transaminase (ALT). The histopathological evaluation also revealed renal tubular dilation and necrosis. Thymic atrophy/reduced thymus weight was observed in 5/8 high dose animals, an effect also noted in the two generation study (see section 3.10.2) and in studies performed with other SCAS (i.e. 6.3.1(02), 6.5(06), and 6.8.2(04)).
The effects described above are considered treatment-related whereas single observations made among high dose animals (i.e. cerebral hemorraghes with thrombosis, bronchointerstitial pneumonia and thymic atrophy with lymphoid depletion) are considered to be of unclear significance. According to the study author, these findings (and also the renal effects) are likely to be secondary to dogs being debilitated. It is noted however that thrombosis (atrial) was observed also in studies with silver zinc zeolite (6.4.1(02) and 6.5(05)
The NOAEL is set at 200 mg/kg bw/day based on the pigmentation and hepatic inflammation observed in animals administered 400 mg/kg bw.
From the silver content and the release at pH4 (37°C), the estimated amount of silver ion equivalents at this dose is 5 mg Ag+/kg bw/day. Based on this information, a NOAEL of 179 mg/kg bw/d can be estimated for silver zeolite.

Rats: There is no repeated dose toxicity study in rats performed with the type of silver sodium zirconium hydrogen phosphate considered in the BPR review, i.e. AlphaSan RC2000. However, the repeated dose toxicity of a different type, AlphaSan RC5000, was investigated in CD rats. Based on the chemical composition of AlphaSan RC2000 and RC 5000, the only difference expected to have a significant impact on the toxicity is the silver content which is lower in AlphaSan RC5000 compared to AlphaSan RC2000.
All rats survived treatment with 30, 300 or 1000 mg AlphaSan RC5000/kg bw/day and there were no clinical signs observed. Increased ALP levels, discoloration of pancreas and the Harderian gland were observed in both high and mid dose animals. According to the study author, the discoloration and effects on the Harderian gland (congestion, fibrosis and inflammatory cells) in females administered 300 or 1000 mg/kg bw was due to the blood sampling procedure. It is noted though that results of a rat study performed with silver lactate/silver nitrate (6.3.1 (04) indicate that deposition of silver in many structures of the eye may occur at systemic doses of silver that are insufficient to cause visible agyria in rats. It thus seems possible that the discoloration observed in the Harderian gland in females administered 300 and 1000 mg/kg bw respectively is due to deposition of particulate silver.
Other effects noted among high and mid dose animals included an increase in red blood cells and cholesterol (males only) and changes in organ weights. The absolute weight of spleen was reduced in mid and high dose males but increased in mid and high dose females. Due to the inconsistency between sexes, this difference is not considered to be of toxicological significance. The relative heart weight was increased in high dose animals but the increase was only statistically significant in males (cardiac effects are discussed further in the section below). The absolute weights of testes and epididymides were reduced in mid and high dose animals (for epididymides this reduction was only statistically significant for the right organ). In the absence of histopathological findings the significance of these effects are unclear.
The NOAEL was set at 30 mg/kg bw based on the increased level of ALP in females and the pigmentation of the Harderian gland observed in all animals administered 300 mg/kg bw. This corresponds to approximately 0.3 mg silver ion equivalents/mg/kg bw/day. Using a back-calculation of this NOAEL based on the silver content and 28% release of silver ions, a NOAEL of 21 mg/kg bw/d can be estimated for silver zeolite.

Comment: the study in rats was perfomed with Alphasan RC 5000 which contains less silver than Alphasan RC 2000 and thus can be assumed to be less potent than the representative formulation Alphasan 2000. It may thus be scientifically justified to adjust the NOAEL set for Alphasan RC5000 based on silver content (adjusted value: 11mg/kg bw). However, Alphasan RC 2000 was tested in dogs which are usually more sensitive than rats and the results indicate a much higher (less conservative) NOAEL (200 mg/kg bw/d) than the NOAEL set in the rat study with AlphaSan RC 5000.
Moreover, taking into account that there is a tenfold difference between the NOAEL and LOAEL in the rat study with RC5000, it may be argued that even if the LOAEL for RC 2000 would be lower than 300 mg/kg bw set for RC 5000, this uncertainty is compensated for by the large dose-spacing.
Therefore, the lowest sub-chronic NOAEL which is set for RC 5000 (30 mg/kg bw) is considered to serve, unadjusted, as an overall subchronic NOAEL for the representative formulation RC 2000.

Common effects noted among SCAS:
Comparing the effects noted among studies performed with different SCAS, it becomes clear that some effects are common to all SCAS tested. The most acknowledged effect of silver compounds is the pigmentation of organs and tissues which is observed in all repeated dose toxicity studies performed via the oral route. Undoubtedly, this effect is associated with the silver ion and can be expected for all silver substances releasing silver ions at a certain rate. The effect, denoted argyria, is discussed below along with some other observations made among the studies performed.

Argyria: The toxicological profile of silver has been summarised in various documents and has been assessed by authorities such as the US EPA (U.S. Environmental Protection Agency), ATSDR (Agency for Toxic Substances and Disease Registry) and the Oak Ridge Reservation Environmental Restoration Program. All of the authorities identify agyria, as the most important effect caused by repeated exposure to silver. Argyria can be generalized (a blueish-gray discoloration of the skin, hair and internal organs), localized or restricted to the structures in the eye (argyrosis). The susceptibility to this effect seems to vary between individuals but the lowest dose reported to cause argyria is approximately 1 g silver (in the form of silver arsphenamine) and administered intravenously during 2 to 9 years (study from 1935).
In the open literature, argyria is generally regarded as a cosmetological effect rather than an adverse toxicological effect. However, since it is a permanent condition, it is yet recognised as a toxicologically significant effect. The discoloration is most prominent in areas exposed to the sun, probably due to an increase in melanin production in response to silver deposition.
Biopsy samples taken from affected individuals show deposition also in tissues such as the kidney, liver and the gastrointestinal tract (6.2(04)). Mineral deposits have been observed in basal membranes for macrophages, in the pericurium of the peripheral nerves, along elastic and collagenous fibres and in the necrotic cells of the oral mucosa using light and electron microscopy (6.12.2(05)).
In some respect, silver deposition in tissues could be regarded as an efficient process to detoxify the body following silver exposure (Venugopal & Luckey). However, although the toxicological significance is unclear, it is not safe to exclude that deposition of a heavy metal in the body may lead to adverse effects.

According to human cases of argyria described in the open literature, there seems to be few clinical symptoms associated with the condition. However, a few reports can be found describing isolated cases of hepatic and renal failure (6.12.2(07)), neurological disorders including taste and smell disorders, vertigo and hypaesthesia (6.12.2(05)) and respiratory irritation along with reduced night vision in workers exposed to dusts of silver compounds (6.12.2(08)). The low incidence of clinical conditions reported could reflect a low inherent toxicity of silver compounds but it could also be explained by a low systemic exposure to silver from traditional uses. However, with little or no information with respect to if and/or to what extent argyric patients have been physiologically examined, it is difficult to exclude that effects may have appeared later in life. Therefore, argyria may not be the only toxicological significant effect of silver in humans. In fact, some indications suggesting an association between pigmentation of tissues and adverse toxicological effects can be found among the studies performed with different SCAS:

Cardiovascular system- an increased left ventricular hypertrophy rate was observed in rats administered silver nitrate in drinking water (Olcott (1950), evaluated in an addendum to the toxicological section of Doc IIIA). It was postulated (but not verified) that the cardiac effect was caused by hypertension. Since only a few scattered granular deposits were observed in the heart, it was suggested that the hypertension was due to a thickening of the basement membrane of kidney glomeruli following silver deposition. The Agency for Toxic Substances and Disease Registry (ATSDR) dismissed the study based on the poor experimental design and inadequate reporting of methods and did not consider the study useful to predict equivalent exposure levels in humans. Indeed, the study has limitations however the effects resemble those reported from a study in turkeys (i.e. cardiac enlargement and ventricular hypertrophy) following exposure to 900 mg/kg bw silver nitrate in diet during 18 weeks (study 6.2(04)).
An increased cardiac weight was noted in the 90-day rat study with silver sodium hydrogen zirconium phosphate (6.4.1(04)). There were no accompanying histopathological changes in the heart and the effect was thus not given toxicological significance when considered in isolation. Without any clear association between cardiac and kidney effects (see below) at the silver ion exposure levels achieved in the studies, the concern for secondary effects on the cardiovascular system as a consequence of silver deposition in kidneys is low. However, it cannot be excluded that there may be an association at higher exposures to silver ions.

Alkaline phosphatatse (ALP) and pigmentation- In many studies showing pigmentation of tissues there is also an increased level of circulating serum ALP. This increase does not appear to have a clear correlation with liver damage thus the ethiology of the increase is unclear. Histological examination of caecum/the small intestine of rats administered a different SCAS denoted "reaction mass of titanium dioxide and silver chloride" showed that pigmentation was localised to the capillary basement membrane. It was thus speculated that the increased level of ALP was attributed to damaged capillaries that are rich in ALP (6.3.1(03)). In case pigmentation causes capillary damage in caecum and the small intestine, it seems reasonable to assume that this could occur in any tissue where silver is deposited in the basement membrane. Therefore, increased levels of ALP occurring along with pigmentation of tissues could be interpreted as an indication of cellular damage.

Kidneys- ALP is also found in the renal tubules. Renal pigmentation and/or histopathological changes have been observed in several studies (including the 90 day study in dogs (6.4.1 (05)) thus kidneys seems to be a target organ for silver toxicity. The mechanism of renal toxicity is however difficult to interpret since histopathological changes have been observed both in the presence and

in the absence of pigmentation. Moreover, renal pigmentation has been observed also without accompanying significant histopathological changes (study 6.5 (05, 06)). Consequently, it is difficult to conclude whether or not pigmentation of kidney structures should be regarded as a marker of renal toxicity.
Impaired kidney function of workers exposed to metal silver powder (indicated as increased excretion of N-acetyl-β-D-glucosaminidase and decreased creatinine clearance) has been described in a case report available in the open literature report (6.4.2(03)). However, since the workers were simultaneously exposed to cadmium the results are difficult to interpret. A different published report describes a case of fatal renal and liver failure in a patient following instillation of silver nitrate into the renal pelvis (summarised in 6.12.2-07).

Oxidative stress: According to published research, the silver ion is capable of a direct induction of oxidative stress and intracellular zinc release in human fibroblasts (Cortese-Krott MM et al (2009)). Nanoparticles of silver appear to have even further capacity to induce oxidative stress in cells (Cha et al, Biotecnol Lett (2008)). The reactive oxygen species produced in an oxidative stress response may damage enzymes through peroxidation, cause damage to specific amino acid residues, changes in tertiary structure, degradation and fragmentation. According to Kohen and Nyska (2002), such damage may then cause loss of enzymatic activity, altered cellular functions such as energy production, interference with membrane potential generating processes and cause changes in the protein profile of the cell. Reactive oxygen species may also damage the DNA through modifications of DNA bases, single and double DNA breaks, loss of purines, damage to the deoxyribose sugar, DNA-protein cross-link and damage to the DNA repair systems (Kohen and Nyska (2002)).
As shown in the table above, the actual concentration of silver ion equivalents tested in the repeated dose studies performed is quite low and it is thus possible that any oxidative stress caused by these SCAS can be managed by the cellular defence mechanism. However, continued cellular oxidative stress could theoretically result in long-term effects if the amount of silver ion equivalents exceeds the capacity of the cellular defence mechanisms. This may be reflected in the results from the 90 day dog study (6.4.1(05)) showing pigmentation of liver along with inflammation and necrosis at and above a dose of approximately 10 mg silver ion equivalents/kg bw. As pigmentation was localised to macrophages in the liver it is possible that the inflammation is caused by an increased macrophage activity and thus the oxidative stress.
Silver is an antagonist to selenium, vitamin E and copper (6.2(06), 6.8.1(03)) and people having selenium and/or vitamin E deficiency may be extra sensitive to silver toxicity.

3.6.1.2 Comparison with the CLP criteria

CLP reads "*substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure.*

Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of: reliable and good quality evidence from human cases or epidemiological studies; or observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9), to be used as part of a weight-of- evidence evaluation.

Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6)."

Effects of silver ions:
Pigmentation and haematological changes were noted in 90-day studies with silver zinc zeolite and silver sodium hydrogen zirconium phosphate.
Pigmentation of organs and tissues is a well-known effect of silver ions and has been discussed in terms of classification during the 35th meeting of the Risk Assessment Committee (RAC). The meeting did not consider the effect to fulfil criteria for classification based on the following justification:
"The precipitation of a heavy metal in organisms is an irreversible bioaccumulative process. Since the human health consequences are not known in the case of silver, it is uncertain whether this effect fulfils the severity criterion described in the CLP Guidance."
Consequently, pigmentation which is expected to occur at doses above 21 mg silver zeolite/kg bw/d is not considered to fulfil criteria for classification.
Reduced haemoglobin levels: In the guidance document on haemaolytic anemia prepared within the European Chemicals Bureau (document ECBI/07/03 Add. 11) and in the Guidance to Regulation (EC) No 1272/2008, a reduction of 20 % or more in Hb concentration is considered to be a sufficient stand-alone criterion for haemolytic anaemia.
Since the 20% reduction was observed at a dose level estimated to correspond to a dose of 372 mg Type LGK/kg bw which is above the range for STOT-RE in category 2 (10< C≤ 100 mg/kg bw), criteria are not considered fulfilled.

3.6.1.3 Conclusion on classification and labelling for sub-chronic repeated dose toxicity

In the absence of substance-specific information, a robust classification proposal cannot be presented. However, based on the data available for the individual constituents of silver zeolite, there are no indications raising a concern that silver zeolite has intrinsic properties meeting criteria for classification.

3.6.2 Sub-chronic dermal toxicity

Summary table of dermal sub-chronic animal studies (usually 90-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Vehicle, Dose levels, Surface area, Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
EPA FIFRA Guideline 82-3. GLP Reliability: 2	Rat Sprague-Dawley	Silver copper zeolite 100, 300 and 1000 mg/kg bw/day 90 days	>1000 mg/kg bw (~6.5 mg silver ion equivalents /kg bw)	Effects noted: <u>1000 mg/kg bw</u>: ↓Bodyweight gain*(m, 12%) ↑Severity of histopathological changes in the kidneys (dilated ducts with casts, cysts, atrophic ducts, fibrotic glomeruli). <u>300 mg/kg bw:</u> ↓Bodyweight gain* (m, 8%) <u>100 mg/kg bw:</u> ↓Bodyweight gain* (m, 14%) *not statistically significant	Read across	IIIA 6.4.2(01)

Summary table of human data on sub-chronic dermal toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

There is no substance-specific information available for Type LGK however the sub-chronic dermal toxicity of silver copper zeolite, a similar type of zeolite containing a comparable amount of silver, was tested in a 90-day study in rats. In this study, some effects were noted (i.e reduced bodyweight, reduced white blood cells, reduced ALT/SGPT) but effects were neither consistent between doses and sexes nor statistically significant. Histopathological changes were observed in the kidneys (dilated/atrophic ducts) of high dose animals. Although none of the effects on bodyweight, clinical chemistry parameters or histopathological changes in kidneys were considered adverse, they may indicate that the NOAEL is close to the highest dose tested (i.e. >1000 mg/kg bw).
Since pigmentation of organs and tissues, an early marker of silver exposure, was not observed at the limit dose of 1000 mg silver copper zeolite/kg bw it seems reasonable to assume that reference values set for the oral route would protect from systemic effects following dermal exposure.

Value used in Risk Assessment – Sub-chronic dermal toxicity	
Value/conclusion	NOAEL>1000 mg/kg bw/d
Justification for the value/conclusion	The value is set based on animal data considered to be of sufficient quality.

3.6.3 Sub-chronic inhalation toxicity

Summary table of inhalatory sub-chronic animal studies (usually 90-day studies)						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, form** *(gas, vapour, dust, mist)* **and particle size** (MMAD)**, Actual and nominal concentration, Type of administration** *(nose only / whole body/ head only),* **Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available						

Summary table of human data on sub-chronic inhalation toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in Risk Assessment – Sub-chronic inhalation toxicity	
Value/conclusion	Not applicable
Justification for the value/conclusion	No data available

Data waiving	
Information requirement	No further data required
Justification	In the absence of inhalation studies, it is not possible to exclude that the NOAEL could be lower following inhalation exposure. According to a summary document on zeolite A prepared by HERA 2004 (Doc IIIA Addendum 2- Zeolite A Toxicity), local effects of dust such as focal nonsuppurative inflammatory responses (bronchioloitis and alveolitis) were observed in monkeys exposed to 1, 6 and 50 mg/m^3 for 6 hours, 5 days per week during 6, 12 or 24 months. There was no evidence of progressive pulmonary fibrosis or systemic toxicity in this study and not in other studies performed with Wistar rats, guinea pigs or Syrian hamsters. In the absence of original data, it is only possible to conclude that local inflammation in the lungs can be anticipated following inhalation. However, since the maximum dose (50 µg/L) was far below the limit dose in OECD TG 413 (5mg/L) cannot be excluded that other effects may occur at higher doses. Nevertheless, according to information from the applicant in section 2.10, the actual exposure via inhalation is expected to be very low. Therefore, assuming that industrial workers respect the work-place routines and that the process takes place in nearly closed systems, the eCA does not consider requests for further animal testing justified for the purpose of this review.

3.6.4 Overall conclusion on sub-chronic repeated dose toxicity

Value used in the Risk Assessment – Sub-chronic repeated dose systemic toxicity	
Value	The estimated NOAEL is 21 mg/kg bw/d
Justification for the selected value	See section 3.6.1.1.
Classification according to CLP and DSD	Effects following repeated administration of SCAS are compared to CLP criteria in section 3.6.1.3.

Value/conclusion used in the Risk Assessment – Sub-chronic repeated dose local effects	
Value/conclusion	Not applicable
Justification for the selected value/conclusion	There are no substance-specific studies available. However, since no local effects were observed in the acute studies performed with AgION Antimicrobial Type AD, the NOAELs set for the oral route are considered to cover also for potential local effects.
Classification according to CLP and DSD	Not applicable (see above)

3.7 LONG-TERM REPEATED DOSE TOXICITY

3.7.1 Long-term oral toxicity

Summary table of oral long-term animal studies						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Route of exposure** *(gavage, in diet, other),* **Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No substance-specific data available						

Combined chronic and carcinogenicity Oral Reliability 2-3	Mouse B6C3F1 0.9% 75/sex**	AgION Zeomic AJ 10N (2.3% Ag, 12.5% Zn) 0, 0.1, 0.3 and 0.9% "at least" 0, 67, 211 and 617 mg/kg bw/day 0, 0.67, 2.0 and 6.9 mg silver ion equivalents/kg bw No statistically significant increase of tumours in treated animals.	NOAEL not determined LOAEL: 0.1% (~0.67 mg silver ion equivalents/kg bw)	**<u>0.9%</u>** ↓RBC, HCT, MCH, MCV, Hb ↑MCHC ↑ renal cysts* (M, F) ↑enlargement of Langerhan´s islands (M) ↓kidney (8%), liver (10%), brain, weight (10%) (F) ↑pancreas (19%, M) ↑pigmentation of liver and pancreas **<u>0.3%</u>** ↓HCT, MCV, Hb ↑MCHC (F) ↑ ovarian cysts ↑pigmentation of liver and pancreas **<u>0.1%</u>** ↑ ovarian cysts ↑pigmentation of liver and pancreas ***<u>Other effects;</u>*** ***<u>0.9%</u>*** *↓bodyweight gain <10% (M)* *↑severity of thrombi (M, F)* *↓spleen weight (37%, M)* *↓brain (10%, F)* *0.3%* *↓bodyweight gain <10% (M)* *↓spleen weight (31%, M)* *↓brain (6%, F)* *0.1%* *↓spleen weight (31%, M)*	Read across	

				↓*brain (6%, F)*		
Combined chronic and carcinogenicity Oral Reliability 2-3	Rat 70/sex***	AgION Zeomic AJ 10N (2.3% Ag, 12.5% Zn) 0.01, 0.03, 0.1 and 0.3% ("at least" 0, 3, 9, 30 and 87 mg /kg bw/day)	NOAEL:0.03% (~0.09 mg silver ion equivalents/kg bw) LOAEL: 0.1% (~0.3 mg silver ion equivalents/kg bw)	**<u>0.1 %</u>** ↑Pigmentation of liver, kidneys, pancreas, stomach, lymph nodes choroid plexus ↑ALT (M/F 175/58%), AST (F 96%), ALP (M/F 25/39%), LDL-C (M/F 28/19%) ↑WBC (F 134%) ↓ HCT (10%), MCH (3/3%), MCHC (F 3%), Hb (F 12%) ***Other effects:*** ***<u>all dose levels</u>*** ↑*endometrial polyps* ↑*Severity of hepatic bile duct proliferation* ↓*AST* *(M ≤42%, at 12 months)* ↑*ALT* *(M ≤172%, at 24 months)* ↓*LDH (F≤90%, at 24 months)* ***<u>0.3%</u>*** ↓*thymus weight n.s.s(38%, F)* *0.1, 0.3%* ↓*TP (M ≤10%, M ALB ≤10%* IIIA	Read across Statistically significant positive trends for: Leukemia (m,f) Pituitary adenomas (f)	6.5-06 (1992b)
*dose-response ** Termination: five/sex at 3 months, ten/sex at six months, ten at 22 months and the remaining at 24 months. *** Termination: ten rats/sex at 6 and 12 months and the remaining at 24 months.						

Summary table of human data on long-term oral toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No substance-specific data available				

Value used in Risk Assessment – Long-term oral toxicity	
Value/conclusion	The etimated NOAEL is 6 mg/kg bw/d
Justification for the value/conclusion	See section 3.7.4.1

Data waiving	
Information requirement	No further data is required.
Justification	There is no substance-specific data available for AgION Antimicrobial Type LGK. However, a NOAEL can be estimated if extrapolating the most conservative NOAEL set for an individual constituent of the substance to the dose of AgION Antimicrobial Type LGK needed to achieve this concentration.

3.7.2 Long-term dermal toxicity

Summary table of dermal long-term animal studies						
Method, Guideline, GLP status, Realibility	**Species, Strain, Sex, No/ group**	**Test substance, Vehicle, Dose levels, Surface area, Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available						

Summary table of human data on long-term dermal toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in Risk Assessment – Long-term dermal toxicity	
Value/conclusion	Not applicable
Justification for the value/conclusion	No data available

Data waiving	
Information requirement	No further information required.
Justification	According to information from the applicant, the active substance is handled in industrial processes where personnel use personal protective equipment including disposable masks, gloves and overalls as well as protective glasses. The equipment used is designed to limit human exposure thus the dermal exposure of professional users is expected to be low. Non-professional users and consumers are exposed to silver ions released from treated items but no dermal exposure to the active substance is anticipated. Additionally, since there were no effects observed in a 90-day repeated dose dermal toxicity study performed with AgION Antimicrobial Type AC (see section 3.6), the concern for a different toxicity via the dermal route is low. Consequently further studies are not considered justified.

3.7.3 Long-term inhalation toxicity

Summary table of inhalatory long-term animal studies						
Method, Guideline, GLP status, Reliability	**Species, strain, sex, no/ group**	**Test substance, form** *(gas, vapour, dust, mist)* **and particle size** (MMAD)**, Actual and nominal concentration, Type of administration** *(nose only / whole body/ head only),* **Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available						

Summary table of human data on long-term inhalation toxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Value used in Risk Assessment – Long-term inhalation toxicity	
Value/conclusion	Not applicable
Justification for the value/conclusion	No data available

Data waiving	
Information requirement	No further data required
Justification	In the absence of inhalation studies, it is not possible to exclude that the NOAEL could be lower following inhalation exposure. According to a summary document on zeolite A prepared by HERA 2004 (Doc IIIA Addendum 2- Zeolite A Toxicity), local effects of dust such as focal nonsuppurative inflammatory responses (bronchioloitis and alveolitis) were observed in monkeys exposed to 1, 6 and 50 mg/m^3 for 6 hours, 5 days per week during 6, 12 or 24 months. There was no evidence of progressive pulmonary fibrosis or systemic toxicity in this study and not in other studies performed with Wistar rats, guinea pigs or Syrian hamsters. In the absence of original data, it is only possible to conclude that local inflammation in the lungs can be anticipated following inhalation. However, since the maximum dose (50 µg/L) was far below the limit dose in OECD TG 413 (5mg/L) cannot be excluded that other effects may occur at higher doses. Nevertheless, according to information from the applicant in section 2.10, the actual exposure via inhalation is expected to be very low. Therefore, assuming that industrial workers respect the work-place routines and that the process takes place in nearly closed systems, the eCA does not consider requests for further animal testing justified for the purpose of this review.

3.7.4 Overall conclusion on long-term repeated dose toxicity

Value used in the Risk Assessment – Long-term repeated dose systemic toxicity	
Value	The estimated NOAEL is 6 mg/kg bw/d
Justification for the selected value	See section 3.7.4.1
Classification according to CLP and DSD	Silver zeolite is not expected to have properties meeting criteria for classification.

Value/conclusion used in the Risk Assessment – Long-term repeated dose local effects	
Value/conclusion	No data
Justification for the selected value/conclusion	Not applicable
Classification according to CLP and DSD	Not relevant

3.7.4.1 Short summary and overall relevance of the provided information on long-term repeated dose toxicity

Description of the data submitted:
There is no substance-specific data available. The applicant refers to data obtained with silver zinc zeolite. The sections on chronic toxicity and carcinogenicity in Doc IIIA include 12 different documents but some of these are largely based on the same information.
The most robust data is a chronic/carcinogenicity study in mice and rats performed with the type of silver zinc zeolite denoted AgION Zeomic AJ. Obviously, silver zeolite differs chemically from silver zinc zeolite by the presence of zinc. However, data on silver zinc zeolite is assumed to be "worst-case" for silver zeolite thus read-across is considered justified despite the lack of bridging data.

Chronic toxicity of silver ion equivalents/zeolite:
Although being the most robust data available, the study with silver zinc zeolite type AJ yet suffers from several deficiencies including lack of GLP, lack of statistical analyses for some parameters and some deficiencies in reporting (e.g. tables missing from the study report). Nevertheless, results in this study are in line with those obtained in sub-chronic toxicity studies performed with silver zinc zeolite thus the shortcomings of the studies are not considered to invalidate the results and the use of the study for an assessment of chronic toxicity.
Results mice: AgION Zeomic AJ was administered in diet at daily doses of 0, 0.1, 0.3 and 0.9% corresponding to intake of "at least" 0, 67, 211 and 617 mg/kg bw/day (stated to be the minimum drug intake).
The cumulative survival rate and the mean survival time were similar between treated and control mice. Clinical signs were not tabulated and the information on this parameter is restricted to a sentence stating that abdominal masses and corneal clouding was reported in all mice (including controls) whereas pigmentation of skin was noted in treated animals.
The body weight gain was reduced in the two highest dose groups but the difference was below 10% at all measurements except for weeks 18-65 when body weight gain was reduced by 18% in high dose males compared to controls. Thereafter, the bodyweight gain was higher in high-dose animals compared to controls and at terminal sacrifice (24 months) it was within 10% of the bodyweight gain in female and male control mice.
Effects on hematological parameters (decrease in HCT, Hb, MCV and increase in MCHC) were observed at the two highest dose levels. The gross pathological examinations showed decreased weights of spleen, brain and pancreas as well as pigmentation of liver and pancreas in all treated mice (see table). Thymus was not weighed.
The histopathological examination revealed a statistically significant dose-response of renal cysts in males and females and increased kidney weights of high dose females and enlarged Langerhan´s islands in males. Although the frequency of renal cysts was low and no statistical significance was achieved in pair-wise comparisons, the effect is considered toxicologically significant as the increase was observed in both sexes and effects on kidneys have been observed in other studies (6.4.1 (05-07), 6.4.2(01)).
The total number of cardiac thrombi was identical between control and high dose males but it is noted that the proportion of severe cardiac thrombi was increased in high dose males. Considering that no statistical significance was achieved and that there was no similar effect in females, the observation is not given further significance in this assessment. However, it is noted that an increased frequency of thrombi was observed also in studies 6.4.1(02) and 6.4.1(05).

MICE	**0**	**0.1**	**0.3**	**0.9**
Renal cysts*	M:0/49 F: 0/49	M:0/48 F: 0/49	M:0/49 F: 1/50	M:4/50 F: 3/49
Enlargement of Langer-han´s islands**	M:3/49 F: 0/49	M:7/48 F: 0/549	M:13**/49 F: 0/50	M:11/50** F: 0/49
Ovarian cysts	6/49	22/49**	19/50**	16/49**
* Statistically significant dose response relation ** Statistically significant				

Results rats: Rats received daily doses of 0, 0.01, 0.03, 0.1 and 0.3% corresponding to an intake of "at least" 0, 3, 9, 30 and 87 mg /kg bw/day (minimum drug intake). The cumulative survival rate and the mean survival time in treated animals and controls were similar. Clinical signs were not tabulated and the only information given is a sentence stating that abdominal and subcutaneous masses and corneal clouding was observed in all rats (including controls) whereas pigmentation of skin was noted in treated animals.
Increased levels of liver enzymes (AST, ALT and LDH) and hepatic bile duct proliferation were observed in all treated rats indicating the liver being a target organ. The total count of white blood cells was 2-5 times higher in high dose males and females at 24 months. Effects on hematological parameters (decrease in HCT, Hb (12%), MCH and MCHC) were observed at 24 months in the two highest dose levels in females but there were no effects in males.
There were no effects noted in any of the treated animals at 6 and 12 months or among animals in the lower dose groups at 24 months.
The pathological examination revealed pigmentation of liver, kidneys, pancreas, stomach, lymph nodes and the choroid plexus in high-dose rats.
The chronic NOAEL is set at 0.03% (i.e. 9 mg AgION Type AJ/kg bw/day or 0.09 mg silver ion equivalents/kg bw) based on the pigmentation of organs and tissues. Back-calculating this NOAEL to a NOAEL for silver zeolite (based on the silver content and release) gives a value of 6 mg/kg bw/d.

Conclusion:
There is no substance-specific data on silver zeolite and the long-term effects of silver substances in general are fairly unexplored. A NOAEL for chronic toxicity can be estimated by calculating the NOAEL for silver zeolite that would result in a silver ion exposure that is comparable to the NOAEL set for silver zinc zeolite if assuming that all effects are caused by the silver ion. The results from the chronic/carcinogenicity study performed with silver zinc zeolite indicate an increased frequency of ovarian cysts, pigmentation of liver and pancreas and decreased organ weights in mice and pigmentation of liver, kidneys, pancreas, stomach, lymph nodes and the choroid plexus in rats.
At least pigmentation of organs and tissues seem to be an intrinsic property of the silver ion and to be an early marker of silver toxicity.
The estimated chronic NOAEL for silver zeolite is 6 mg/kg bw/d based on a back-calculation from the NOAEL set for pigmentation in the study with silver zinc zeolite.

3.7.4.2 Comparison with the CLP criteria

CLP states that substances *that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure.*

Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of: reliable and good quality evidence from human cases or epidemiological studies; or observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9), to be used as part of a weight-of- evidence evaluation.

Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basisof observations from appropriate studies in experimental animals in which significant toxiceffects, of relevance to human health, were produced at generally moderate exposureconcentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

Effects of silver ions: the pigmentation of organs and tissues noted in the chronic/carcinogenicity study with silver zinc zeolite is estimated to occur at a dose of silver zeolite falling within the guidance values set for STOT-RE.
Nevertheless, pigmentation of organs and tissues is a well-known effect of silver ions and has been discussed in terms of classification during the 35th meeting of the Risk Assessment Committee (RAC). The meeting did not consider the effect to fulfil criteria for classification based on the following justification:
"The precipitation of a heavy metal in organisms is an irreversible bioaccumulative process. Since the human health consequences are not known in the case of silver, it is uncertain whether this effect fulfils the severity criterion described in the CLP Guidance."
Consequently, the pigmentation expected to occur at doses above 7 mg silver zeolite/kg bw/d is not considered sufficient to fulfil criteria for classification.

3.7.4.3 Conclusion on classification and labelling for long-term repeated dose toxicity

In the absence of substance-specific information, a robust classification proposal cannot be presented. However, based on the data available for the individual constituents of silver zeolite, there are no indications raising a concern that silver zeolite would fulfil criteria for classification.

3.8 GENOTOXICITY

There is no substance-specific information available for silver zeolite. Based on the arguments presented below, the applicant considers waiving justified.

"*Although silver zeolite is theoretically a less complex substance compared to silver zinc zeolite, the possibility of obtaining similar in-vitro and in-vivo results to silver zinc zeolite cannot be ruled out simply based on the absence of zinc. A read across argument to silver zinc zeolite therefore remains uncertain pending additional data*[13].

As an alternative, read across to data on silver chloride/titanium dioxide and silver sodium hydrogen zirconium phosphate can be used to justify a lack of genotoxic potential for silver zeolite. Preliminary conclusions for genotoxicity for these substances are available in the draft human health sections of the respective CAR documents. These documents were issued by the eCA in January 2015. The conclusions for silver chloride/titanium dioxide and silver sodium hydrogen zirconium phosphate are relevant to silver zeolite as these substances, along with silver zeolite, contain silver as the principle element of concern.

The genotoxic potential of silver chloride/titanium dioxide was studied in an in-vivo micronucleus test by [redacted] *(IIIA 6.6.4-01). The conclusions presented in the Human Health section of the preliminary draft CAR were considered at an Early Working Group meeting of Member State experts at ECHA in March 2015. The accepted opinion of the meeting was that silver chloride/titanium dioxide is not genotoxic based on the available in vivo data. The meeting considered there was no clear dose response relationship between the lowest concentrations of silver chloride/titanium dioxide tested and the response (significant) seen at the highest dose. Furthermore, the significance of the response at the highest dose was disregarded as it was within the historical control range.*

The genotoxic potential of silver sodium hydrogen zirconium phosphate was studied in-vivo in micronucleus tests by [redacted] *(IIIA 6.6.4-02) and* [redacted] *(IIIA 6.6.4-03) and in a UDS assay by* [redacted] *(IIIA 6.6.4-04). The result of each study was negative. The Human Health section of the preliminary draft CAR concluded that mutagenicity had been investigated in line with the recommended guidance and the results showed that criteria for classification were not fulfilled.*

These results can be used in a read across argument for silver zeolite with sufficient confidence to avoid the need for additional vertebrate testing.

Silver availability data presented in Section IIIA 3.5 supports a read across argument. Silver zeolite has significantly lower silver availability compared to silver sodium hydrogen zirconium phosphate, lower silver availability compared to silver chloride/titanium dioxide at pH 8 and higher silver availability at pH4. Negative in-vivo genotoxicity results are available for both silver sodium hydrogen zirconium phosphate and silver chloride/titanium dioxide. Therefore, considering exposure to silver is the principle concern there is a high likelihood that if tested in micronucleus and UDS assays silver zeolite would behave in a similar manner to silver sodium hydrogen zirconium phosphate and silver chloride/titanium dioxide and produce a negative response in-vivo in micronucleus and UDS type assays."

13 This additional data (i.e. an alkaline comet assay in the rat) was received in January 2017 and is discussed in 3.8.2.

eCA comments on read across:
Principally, read across can be accepted as this approach has been taken also for other endpoints. However, the strategy used in this assessment is to assess the toxicity of each individual constituent of silver zeolite and conclude based on the most conservative value in order to compensate for the inherent uncertainty of the approach. Structurally, silver zeolite is more similar to silver zinc zeolite and silver copper zeolite than to the other SCAS. Therefore, data available for these substances are considered more relevant despite the presence of additional metal ions (i.e. zinc and copper). The data available for other SCAS gives supplementary information on the genotoxic potential of the silver ion but is insufficient as the zeolite part also needs to be addressed.

3.8.1 In vitro

Summary table of in vitro genotoxicity studies					
Method, Guideline,GLP status, Reliability	**Test substance, Doses**	**Relevant information about the study** *(e.g. cell type, strains)*	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
Silver zeolite Type AK					
Ames/Salmonella Mutagenesis Assay EC: A6.6.2 US EPA: 84-2, 870.5100 GLP Reliability: 1-2	Silver Zinc Zeolite Type AK 0.15, 0.5, 1.5, 5, 15, 50, 150 and 500 µg/plate with and without S9	S. typhimurium and E. coli	Negative	Bacterial toxicity evident at dose concentrations of 500 µg/plate and higher	IIIA 6.6.1-11
Mammalian cell mutation Forward mutation at TK locus EU: 2000/32/EC Annex 4E- B17 USA EPA: 870.5300 GLP Reliability: 1	Silver Zinc Zeolite Type AK 0 to-25 µg/ml without S-9 and 0 to 175 µg/ml with S-9	Mouse lymphoma L5278Y cells	Positive	Cytotoxicity at 10 µg/mL and higher without S9. Cytotoxicity at 100 µg/mL and higher with S9 Positive response within cytotoxic dose ranges with or without S9 Tendency towards an increase in % small mutant colonies, indicating a possible clastogenic effect.	IIIA 6.6.3-03
Silver zinc zeolite					

Ames/Salmonella Mutagenesis Assay EPA FIFRA Guideline 84-2 GLP Reliability: 2	Silver zinc zeolite 4% silver Without S9: 0.0005, 0.001, 0.0015, 0.003, 0.005, 0.01 and 0.015 mg/plate. With S9: 0.003, 005, 0.01, 0.015, 0.03, 0.05 and 0.15 mg/plate	The ability to detect DNA cross-linking mutagens was not investigated.	Negative	In the non activated assay, bacterial toxicity was evident at concentrations in excess of 0.015 mg/plate (noted as decreased mean no of revertants compared to water control) and at concentrations greater than 0.15 mg/plate in the activated assay.	IIIA 6.6.1-03
Mammalian cell mutation Forward mutation at TK locus OECD 476 GLP Reliability: 1	Irgaguard B 8000 Dose levels, selected on the basis of preliminary test results: Assay 1, without S9: 3.1, 6.3, 12.5, 25.0 and 50 µg/mL in Assay 1 with S9: 13.1, 26.3, 52.5, 105.0 and 210.0 µg/mL in Assay 2 without S9: 6.3, 12.5, 25.0 and 50 µg/mL in	Mouse lymphoma L5278Y cells	Negative (+S9) Positive (-S9)	An increase in the number of small colonies observed indicating a possible clastogenic activity.	IIIA 6.6.3-05
In vitro chromosome aberration test OECD 473 GLP Reliability: 1	Irgaguard B 8000 Without S9: **0.9, 1.9, 3.8, 7.5,** 15,30 µg/mL With S9: **6.3, 12.5, 25.0, 50.0,** 75.0, 100 (evaluated concentrations in bold)	Chinese Hamster V79 cells	Negative (+S9) Positive (-S9)		IIIA 6.6.2-07
Silver copper zeolite					
Ames/Salmonella Mutagenesis Assay EPA Guideline 84-2 GLP Reliability: 2	Silver copper zeolite With S9: 0.005, 0.015, 0.05, 0.15, 0.5 and 1.5 mg/plate Without S9: 0.0005, 0.01, 0.015, 0.03, 0.05, 0.1 and 0.15 mg/plate.		The test material was non-mutagenic at all concentrations tested in the two assays.	The ability of silver copper zeolite to cross-link DNA was not investigated in this study.	IIIA 6.6.1-06

In vitro chromosomal aberration assay in CHO cells EPA FIFRA 84-2 GLP: Yes Reliability: 2-3	Silver copper zeolite For non activated assay: 0.5, 1.0, 1.5, 3, 5, 10, 15, 30, 50 and 100 µg/mL Activated assay 1: 10 hr - 1, 1.5, 3, 5, 10, 15, 30, 50, 100, 150 and 500 µg/mL 20 hr - 0.15, 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/mL Activated assay 2: 10 hr - 10, 25, 50, 75, 100, 125 and 150 µg/mL 20 hr - 10, 25, 50, 75, 100, 125 and 150 µg/mL		+S9: Weakly positive at 100 µg/mL -S9: Negative	Toxicity was observed in the 10 h non-activated assay at 30, 50 and 100 µg/mL and in the 20 h non-activated assay at 100 µg/mL. In the 10 h activated assay, toxicity was observed at 150 and 500 µg/mL in the initial assay and at 150 µg/mL in the replicate. For the 20 h activated assay, toxicity was apparent at concentrations of 150, 500, 1500 and 5000 µg/mL and at 150 µg/mL in the replicate assay.	IIIA 6.6.2-05

Conclusion used in Risk Assessment – Genotoxicity *in vitro*	
Conclusion	Silver zeolite is expected to be genotoxic in vitro.
Justification for the conclusion	Results obtained with similar substances, i.e. silver zinc zeolite and silver copper zeolite, indicate that the substance is clastogenic in vitro.

3.8.2 In vivo

Summary table of in vivo genotoxicity studies					
Method, Guideline, GLP status, Realibility	**Test substance, Doses**	**Relevant information about the study** *(e.g. species and strain, duration of exposure)*	**Observations**	**Remarks** *(e.g. major deviations)*	**Reference**
In vivo chromosome aberration assay in rats EPA FIFRA 84-2 GLP: Yes Reliability: 2-3	silver zinc zeolite 500, 1500 and 5000 mg/kg	Rats Sprague-Dawley 5/sex Single oral dose (gavage,) 6h, 18h, 24h post exposure	Negative	Unclear exposure of target tissue; no signs of toxicity at doses up to dose of 5000 mg/kg bw. The sampling time was not optimal. Only 50 metaphase cells were scored per animal. According to OECD guideline, at least 100 metaphase cells should be scored	IIIA 6.6.4-01
In vivo chromosome aberration assay in rats EPA FIFRA 84-2 GLP: Yes Reliability: 2	Single oral dose (gavage) 500, 1500 and 5000 mg/kg	Sprague-Dawley rats 5/sex Sampling time: 6h, 18h, 24h post exposure	Negative	No signs of toxicity in the target tissue at any dose level.	IIIA 6.6.4-02
Rat Alkaline Comet Assay OECD 489 (2014) *GLP* *Reliability 1*	*Hygentic 8000* *Silver zinc zeolite* *0, 500, 1000 and 2000 mg/kg bw* *Administered as 2 doses separated by 21 hours*	*Han Wistar Crl:WI males* *6 animals/dose* *3 controls*	*No evidence of genotoxicity in tissues analysed (liver, stomach or duodenum)*	*This result is considered relevant to assess the genotoxic potential of the silver and zeolite in silver zeolite*	*IIIA* *6.6.5-02* *(separate document)*

Summary table of human data on genotoxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in Risk Assessment – Genotoxicity *in vivo*	
Conclusion	Silver zeolite is not expected to be genotoxic in vivo.
Justification for the conclusion	The positive in vitro findings were followed up in an alkaline Comet Assay. The results from this study did not indicate a genotoxic potential of silver zinc zeolite. Consequently, silver zeolite is not expected to be genotoxic in vivo.

3.8.3 Overall conclusion on genotoxicity

Conclusion used in the Risk Assessment – Genotoxicity	
Conclusion	Silver zeolite is not expected to be genotoxic in vivo.
Justification for the conclusion	Based on weight of evidence from data on silver zinc zeolite and silver copper zeolite, the genotoxicity observed in vitro is not expressed in vivo.
Classification according to CLP and DSD	Data is insufficient for a robust classification proposal.

3.8.3.1 Short summary and overall relevance of the provided information on genotoxicity

The bactericidal activity of silver involves damage of several cellular structures. The silver ion may cause the cytoplasm membrane to detach from the cell wall and inside the cell it can bind and structurally alter enzymes via available thiol groups. The bacteria appear to have defence systems, which protects the genetic material from the silver ion. However, at dose levels exceeding the defence capacity, the silver ion is able to interact with DNA whereupon the DNA becomes condensed preventing replication (Feng et al. (2000), Jung et al. (2008). This mechanism may protect the genetic material from being propagated with mutations.

In vitro: The genotoxicity of silver zinc zeolite and silver copper zeolite was investigated in an Ames test and in an *in vitro* chromosome aberration test. Silver zinc zeolite was also tested in the mammalian cell mutation test. There was no increase of revertants in the Ames test but a slight increase of chromosome abberrations was observed in CHO cells, both with silver zinc zeolite and with

silver copper zeolite. A positive result was also observed in the mammalian cell mutation tests, both with type AK and with Irgaguard B 8000. Therefore silver zinc zeolite and silver copper zeolite were considered genotoxic in vitro and consequently silver zeolite is expected to share this property.

In vivo: no indications of genotoxicity were observed in the two *in vivo* chromosome aberration assays performed but exposure of target tissue could not be demonstrated and confidence in the result is thus low. Considering the low oral absorption and biliary elimination of silver substances (see, section 3.1), the majority of the substances is eliminated before reaching the systemic circulation. Moreover, the sampling time used in the study with silver zinc zeolite was not optimal. According to OECD guideline, samples should be taken at two separate times following treatment on one day. For rodents, the first sampling interval is 1.5 times the normal cell cycle length which is normally 12-18 hr following treatment. Since both the time required for uptake and metabolism of the test substance and its effect on cell cycle kinetics can affect the optimum time for chromosome aberration detection, a later sample collection time (24 hr after the first sample) is recommended. In essence, this implies that any genotoxic effects would only be detected at a sampling time after 24 h (under the prerequisite that enough amounts of the test substance reached the target tissue).
Due to these uncertainties, the results from the in vivo chromosome aberration assays are considered insufficient to dismiss the concern for genotoxicity raised from the in vitro studies.
BPR guidance states[14] *"For substances that are short-lived, reactive, in vitro mutagens, or for which no indications of systemic availability have been presented, an alternative strategy involving studies to focus on tissues at initial sites of contact with the body should be considered (e.g. local genotoxicity, photomutagenicity). Expert judgment should be used on a case-by-case basis to decide which tests are the most appropriate. The main options are the in vivo Comet assay, gene mutation tests with transgenic rodents, and DNA adduct studies. For any given substance, expert judgment, based on all the available toxicological information, will indicate which of these tests are the most appropriate."*
Furthermore, the REACH guidance[15] advices (figure R.7.7–1) *"For evidence of clastogenicity, a micronucleus test, a chromosome aberration test or a comet assay would be the appropriate follow up test; whereas for evidence of gene mutations, a transgenic rodent gene mutation assay, a comet assay, or in some cases an unscheduled DNA synthesis test would be the appropriate follow up test."*
To further address the possible in vivo genotoxic potential of silver zinc zeolite, the applicant conducted an (in vivo) alkaline comet assay. The alkaline comet study was performed in rat using a silver zinc zeolite denoted Hygentic 8000 (considered to represent silver zinc zeolite, further discussed in the CA report for silver zinc zeolite).

14 Guidance on the Biocidal Products Regulation, Volume III: Human health, Part A: Information Requirements (Version 1.1, November 2014)
15 Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance (Version 5.0, December 2016)

Male rats received two doses of 0, 500, 1000 or 2000 mg/kg bw separated by 21 hours. Positive controls received EMS. The tissues selected for comet analysis included the liver (as the primary organ for metabolism) and the stomach and duodenum (as the key sites of contact following oral administration).
The results of the analyses of liver, stomach and duodenum in treated animals were comparable with the group mean vehicle control data (i.e. no statistically significant increases in tail intensity between treated and control groups).
Some microscopic changes related to administration of the test article were observed in the stomach and liver and an increase in mean glucose concentration was also observed. These changes were not considered to impact on the comet analysis of the tissues.
Based on these results, Hygentic 8000 does not induce DNA damage in the liver, stomach or duodenum of male rats following oral administration of doses up to 2000 mg/kg bw (the maximum recommended dose for in vivo comet studies).
Consequently, the applicant has fulfilled the data requirement to follow up positive in vitro findings with an appropriate in vivo assay. **Since a negative result was obtained, silver zinc zeolite and consequently also silver zeolite are not considered genotoxic in vivo.**

Data available for other silver containing active substances (SCAS) in the dossier:
The dossier contains in vitro and in vivo genotoxicity data for three additional but chemically different SCAS; reaction mass of titanium dioxide and silver chloride (JMAC), silver sodium hydrogen zirconium phosphate and silver zinc zeolite.

In vitro: All tested SCAS show similar responses *in vitro*, i.e. a negative response in Ames/Salmonella mutagenesis assay, indications of positive response in mammalian mutation assays at the thymidine kinase TK+/- locus, and/or in chromosome aberration assays (in CHO cells). In several tests, the positive response in the thymidine kinase TK+/- locus assay was coupled to an increase in the number of small colonies, which may be a sign of a possible clastogenic activity. Positive responses occurred mostly at cytotoxic concentrations and the cytotoxicity was more profound at lower doses without metabolic activation. The positive response in CHO cells observed in a test with JMAC was not reproduced in a second experiment. A negative response was obtained in a chromosome aberration assay in CHO cells (performed with Irgaguard 8000, i.e., one form of silver zinc zeolite), in a chromosome aberration assays in human lymphocytes (performed with silver sodium hydrogen zirconium phosphate), and in a mammalian mutation assays at the thymidine kinase TK+/- locus (performed with JMAC).
Overall, the in vitro data for the SCAS tested appear to exhibit a genotoxic response in vitro.

In vivo: The additional in vivo data include micronucleus assays performed with silver sodium hydrogen zirconium phosphate and reaction mass of titanium dioxide and silver chloride (JMAC) and a liver unscheduled DNA synthesis assay with silver sodium hydrogen zirconium phosphate. In similarity with the studies performed with silver zinc zeolite and silver copper zeolite, target tissue exposure could not be demonstrated in the micronucleus study with silver sodium hydrogen zirconium phosphate, there was no evidence that test substances reached the target tissue in quantities sufficient to enabling detection of genotoxic effects.

Conclusion on data available for other SCAS: Preferentially, target tissue exposure should be demonstrated by indications of toxicity in the target tissue or secondly, by robust toxicokinetic data ensuring that test substance most likely reaches the target tissue. No such toxicokinetic data is availble for the silver substances tested. According to the data presented in the section on toxicokinetics,

the highest concentrations of silver orally absorbed from silver nitrate and silver chloride are found in the reticuloendothelial tissues (liver, spleen, bone, lymph nodes, skin and kidney) of the rat. However, even though this may indicate that the target tissue was exposed to the test substances, uncertainty remains if this really was the case in the present studies.
It should be noted that, according to Olcott (1948), a few black granules were observed in the bone marrow of rats but it was not possible to determine whether or not this was silver and the bone marrow of rats exposed to silver or water appeared the same.
Target tissue exposure was observed in one of the oral in vivo studies performed with silver sodium hydrogen zirconium phosphate, and in one of the tests performed using i.p injection of JMAC. The results from both assays were negative.
However, silver zeolite (as well as silver copper zeolite and silver zinc zeolite) differs chemically and possibly toxicologically from the other silver substances. Besides obvious differences in composition (metal ions and the zeolite matrix), also the release of silver ions and thus the actual silver ion exposure may differ. Therefore, the information above is considered to have limited relevance for the assessment of silver zeolite.

3.8.3.2 Comparison with the CLP criteria

The criteria reads *"This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class (3.5.2.1)."*
For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories as shown in Table 3.5.1 (3.5.2.2).
"Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans.
Category 1A: The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.
Category 1B: The classification in Category 1B is based on:
— positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or
— positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
— positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
Category 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans
The classification in Category 2 is based on:
— positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
— somatic cell mutagenicity tests in vivo, in mammals; or
— other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.

Note: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens."
The CLP guidance further states:
"It is also warranted that where there is evidence of only somatic cell genotoxicity, substances are classified as suspected germ cell mutagens. Classification as a suspected germ cell mutagen may also have implications for potential carcinogenicity classification. This holds true especially for those genotoxicants which are incapable of causing heritable mutations because they cannot reach the germ cells (e.g. genotoxicants only acting locally, 'site of contact' genotoxicants). This means that if positive results in vitro are supported by at least one positive local in vivo, somatic cell test, such an effect should be considered as enough evidence to lead to classification in Category 2. If there is also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied."

The *in vitro* test in mammalian cells indicate a genotoxic potential of silver zinc zeolite and silver copper zeolite that cannot be dismissed by the results from the follow-up in vivo chromosome aberration test since exposure of target tissue was not demonstrated. However, since the second *in vivo* test, the alkaline comet assay in rat, did not indicate a genotoxic potential of silver zinc zeolite, the criteria for classification in category 2 are not fulfilled. Data on silver zinc zeolite is considered to be conservative with respect to silver zeolite and AgION Antimicrobial Type LGK is thus not expected to fulfil criteria for classification.

3.8.3.3 Conclusion on classification and labelling for genotoxicity

The *in vitro* tests in mammalian cells indicate a genotoxic potential of silver zinc zeolite and silver copper zeolite which was not expressed in the *in vivo* comet assay performed with silver zinc zeolite. Consequently, silver zinc zeolite and by read-across silver zeolite is not expected to meet criteria for classification.

3.9 CARCINOGENICITY

Summary table of carcinogenicity studies in animals						
Method, Guideline, GLP status, Realibility	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Route of exposure, Duration of exposure**	**NOAEL, LOAEL**	**Results** *(Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects)*	**Remarks** *(e.g. major deviations)*	**Reference**
Summary References: Reliability 3						IIA 6.5(01) 6.7(01) Plautz, J. and Trendelenburg, C.F. (2005):
Olcott, C.T. Experimental argyrosis. V. Hypertrophy of the left ventricle of the heart. Archives of Pathol. 49: 138-149, 1950.	Rat albino	0.1% silver nitrate (60 or 89* mg/kg bw/day Oral (drinking water) 218 days		↑proteinuria ↑increase in the incidence of ventricular hypertrophy		
*0.1% silver nitrate has been converted to a dose of 60 mg/kg bw in 6.5(01) and 89 mg/kg bw in 6.2(03).						
	B6C3F1 mice (300/sex) Fischer 344 rats (350/sex)	Antibacterial Zeolite Zeomic Silver content 2.6% average zinc content 14.5%. mice: 0.1%, 0.3% and 0.9% rats : 0.01, 0.03, 0.1 and 0.3% Oral (in diet)		See 6.5(05) and 6.5(06) The document seems to be a published report of the study presented in 6.5(05) and 6.5(06). The document does not add any further information than what is presented below.	Article in Japanese, only abstract available in English.	IIIA 6.5(02) 6.7(03) Japanese Journal of Food Chemistry Vol 2 (1) 1995

Reliability 3-4	Rat albino Wistar 40m (after 10 weeks half of the animals were further exposed for 6 months, the rest for 12 months)	0.25% silver nitrate (stated to be 222 mg/kg bw/d in 6.5(04)) Daily exposure 9 months Oral (drinking water)		Rapid weight loss from week 23 onwards and eventually death. Rats surviving to 37 weeks had lost approximately 50% of their maximum weight (reversibility demonstrated) massive accumulation of silver particles in the outer aspect of the ciliary epithelium basement membrane	Tumour development not investigated	IIIA 6.5(03) Matuk, Y. Gosh, M. and McCulloch, C. (1981): Distribution of silver in the eyes and plasma proteins of the albino rat. Handbook on the toxicology of Metals. Can. J. ophthalmol 16.
Reliability not relevant	Rat Human	Various routes		The document summarises results by Matuk (in 6.5(03), Olcott (6.5(01) and addendum 1), case reports of argyria following chronic exposure and the reference dose derived by US EPA (discussed in the section on acceptable exposure level).	Tumour development not investigated	IIIA 6.5(04) Faust, R. (1992) Published report prepared for the Oak Ridge Reservation Environmental Restoration Program

Combined chronic and carcinogenicity OECD 453 EPA 870.4300 EC 87/302/EEC DACO 4.4.4 GLP: no information Reliability: 2-3	Mouse B6C3F175/sex*	AgION Zeomic AJ 10N (2.3% Ag, 12.5% Zn) 0, 0.1, 0.3 and 0.9% "at least" 0, 67, 211 and 617 mg/kg bw/day 0, 0.67, 2.0 and 6.9 mg silver ion equivalents/kg bw Oral	NOAEL not determined LOAEL: 0.1% (~0.67 mg silver ion equivalents/kg bw)	**No statistically significant increase of tumours in treated animals.** <u>0.9%</u> ↓RBC, HCT, MCH, MCV, Hb ↑MCHC ↑ renal cysts* (M, F) ↑enlargement of Langerhan´s islands (M) ↓kidney (8%), liver (10%), brain, weight (10%) (F) ↑pancreas (19%, M) ↑pigmentation of liver and pancreas <u>0.3%</u> ↓HCT, MCV, Hb ↑MCHC (F) ↑ ovarian cysts ↑pigmentation of liver and pancreas <u>0.1%</u> ↑ ovarian cysts ↑pigmentation of liver and pancreas ***Other effects;*** <u>*0.9%*</u> ↓*bodyweight gain <10% (M)* ↑*severity of thrombi (M, F)* ↓*spleen weight (37%, M)* ↓*brain (10%, F)*		IIIA 6.5-05 (1992a)

				<u>0.3%</u> *↓bodyweight gain <10% (M)* *↓spleen weight (31%, M)* *↓brain (6%, F)* *<u>0.1%</u>* *↓spleen weight (31%, M)* *↓brain (6%, F)* *dose-response		

Combined chronic and carcinogenicity OECD 453 EPA 870.4300 EC 87/302/EEC DACO 4.4.4 GLP: no information Reliability: 2-3	Rat70/sex**	AgION Zeomic AJ 10N (2.3% Ag, 12.5% Zn) 0.01, 0.03, 0.1 and 0.3% ("at least" 0, 3, 9, 30 and 87 mg /kg bw/day) Oral 105 weeks	NOAEL: 0.01 % (~0.03 mg silver ion equivalents/kg bw/day)	**Statistically significant positive trends for:** **Leukemia (m,f)** **Pituitary adenomas (f)** ***Endometrial polyps*** <u>0.1 %</u> ↑Pigmentation of liver, kidneys, pancreas, stomach, lymph nodes choroid plexus ↑ALT (M/F 175/58%), AST (F 96%), ALP (M/F 25/39%), LDL-C (M/F 28/19%) ↑endometrial polyps ↑WBC (F 134%) ↓ HCT (10%), MCH (3/3%), MCHC (F 3%), Hb (F 12%) <u>0.03%</u> ↑endometrial polyps ***Other effects:*** <u>*all dose levels*</u> ↑*Severity of hepatic bile duct proliferation* ↓*AST* *(M ≤42%, at 12 months)* ↑*ALT* *(M ≤172%, at 24 months)* ↓*LDH (F≤90%, at 24 months)* <u>*0.3%*</u> ↓*thymus weight*		IIIA 6.5-06 (1992b)

				n.s.s(38%, F) *<u>0.1, 0.3%</u>* *↓TP (M ≤10%, M ALB ≤10%*		
* Termination: five/sex at 3 months, ten/sex at six months, ten at 22 months and the remaining at 24 months. ** Termination: ten rats/sex at 6 and 12 months and the remaining at 24 months.						

Reliability 3	Rats	Colloidal silver, 14 months Intravenous subcutaneous		Fibrosarcomas Local sarcomas may arise due to solid state carcinogenesis. (however, according to the ATSDR in 6.2 (08), subcutaneous imbedding of silver foil produced fibrosarcomas earlier and more frequently than several other metal foils). 8/26 (type not specified) 6/8 tumours claimed to be at the site of injection, The frequency of other tumours (2/26) appears to be above the spontaneous frequency of 1-3% at any site. No further analysis possible due to poor data (Schmahl and Steinhoff (1960)).	The document summarises information on carcinogenicity found in the IRIS Background document	IIIA 6.5(07) 6.7 (02) Anon. (1998): US EPA Integrated Risk Information SystemReference dose for chronic oral exposure.

Reliability 3	Fischer 344 rats 25/sex/ group	Metal powder suspended in trioctanoin5 or 10 mg per dose (each animal was treated for five consecutive months at 5 mg/dose, ten for five months at 10 mg/dose, then at 5 mg/dose for the subsequent five months and lastly at 10 mg/dose for the last five months). intramuscular		No fibrosarcomas developed at the injection sites for silver. A few cases of mild local inflammation were noted at injection sites but only in the latter stages of the study. At necropsy there were several incidences of encapsulation of the vehicle or injected metal powder but none of the injected legs showed muscular atrophy.		IIIA 6.7 (04) Furst, R. and Schlauder, M.C. (1977): Inactivity of two noble metals as carcinogens. J Environ Path Toxicol 1 Environ.Health Perspect 40.
Various	Rat	Colloidal silver dose and number of animals unknown		Inconclusive (no information about frequency in controls)	The document summarises effects of metals observed in different studies. Information relevant for silver is limited to a sentence staiting that weekly injections of colloidal silver in rats have resulted in a few tumors (Schmahl and Steinhoff (1960).	

Summary table of human carcinogenicity data				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No evidence of cancer in humans has been reported.				IIIA 6.5(07) 6.7 (02) Anon. (1998): US EPA Integrated Risk Information SystemReference dose for chronic oral exposure.

Conclusion used in Risk Assessment – Carcinogenicity	
Value/conclusion	Silver zeolite is not expected to have a carcinogenic potential meeting criteria for classification.
Justification for the value/conclusion	Data obtained with silver zinc zeolite Type AJ in rats show statistically significant positive trends for leukemia in males and females and pituitary adenomas in females. However, as discussed below, these effects were dismissed by RAC at the 35th RAC meeting (December 2015).
Classification according to CLP and DSD	Based on read across to silver zinc zeolite Type AJ, silver zeolite is not expected to have a carcinogenic potential meeting criteria for classification.

Data waiving	
Information requirement	No further data required.
Justification	The carcinogenic potential of silver zeolite can be estimated based on data from silver zinc zeolite.

3.9.1.1 Short summary and overall relevance of the provided information on carcinogenicity

There is no substance-specific data available. However, the carcinogenic potential of the individual constituents of the active substance, i.e. silver ions and the zeolite, is indirectly tested in a chronic toxicity/carcinogenicity study performed with silver zinc zeolite type AJ. Therefore, the carcinogenic potential of silver zeolite may be assessed from the results of this study. The information relevant for carcinogenicity is discussed below whereas the chronic part of the study is summarised in section 3.7.
Mice: at termination, the total number of tumours per animal was lower in high dose males (1.00) compared to controls (1.26) and comparable between high dose females and controls.

A statistically significant increase in the incidence of ovarian cysts was evident although there was no clear dose-response. The frequency was increased already in the low dose group.
Based on the results of this study, AgION type AJ is not considered carcinogenic in mice.

Rats: At termination, the total number of tumours per animal was lower in high dose males (1.86) compared to controls (1.96). In contrast, a higher number of total tumors was observed in high dose females (2.11) compared to controls (1.37) but the difference was not statistically significant.
The statistical analysis did however reveal a dose-related increase in the frequency of leukemia and infiltration of leukemia cells into different tissues in both male and female rats.
Since the tumorous/non-tumorous changes observed were combined for scheduled and intercurrent deaths, it is not clear when in time the leukemia developed.
The increased frequency of leukemia was dismissed by the study author since the frequency was claimed to be within the range observed in historical control data (referred to as Tajima Y, Data of biological characteristics of experimental animals, Soft Science Inc., 1989). While historical control data may be useful when analysing deviations in isolated data points, it is not considered appropriate to disregard a positive trend based on historical data.
The P values obtained in a Cochran-Armitage trend test are 0.026 and 0.019 (one sided) for females and males, respectively. The positive trend is thus clearly statistically significant and it is considered unlikely that this would arise in both males and females in the absence of a true effect. According to the study report, tissues from the right femoral bone were collected but it is not clear if the bone marrow was analysed for histopathological changes.
According to the study report, the dose related increase in pituitary adenomas and endometrial polyps observed in females were statistically significant but the findings were dismissed by the study authors since they were irregularly distributed and lower than the incidence in the historical control data referred to.
In similarity with the line of reasoning for leukemia, it is not considered accurate to dismiss a statistically significant trend by historical control data (especially since the historical control data referred to is not included in the report). The pituitary adenomas observed are therefore regarded as being related to treatment.
However, the positive trend for endometrial polyps was dismissed by the Technical Meeting for Biocides in June 2013 (CAR silver zinc zeolite) thus it is not given further significance here.
The NOAEL for increased incidence of leukemia and pituitary adenomas in females would be 0.1% (i.e. 30 mg AgION Type AJ/kg bw/day or 0.28 mg silver ion equivalents/kg bw) since the dose-response is no longer statistically significant when the highest dose group is excluded from the analysis.
However, as further discussed below, RAC has discussed the results from this study and concluded that the data do not fulfil criteria for classidication in category 2.
In line with this conclusion, silver zeolite is not expected to have a carcinogenic potential and there is thus no need for a NOAEL for carcinogenicity.

Information available of relevance for the carcinogenic potential of silver ions: according to reports available in the open literature, little is known about the carcinogenic potential of silver but human exposure to silver has not been associated with cancer. However, consumer uses of silver compounds and thus exposure scenarios are changing with emerging uses in textiles and treated plastic articles and it is not considered safe to rely on a historical "safe use"of silver. The exposure to silver ions released from elemental silver in jewellery may differ significantly from the exposure to silver ions released from a dental mouth guard containing a silver substance. Moreover, while earlier use of silver mainly resulted in exposure of workers in the photoindustry, future uses in various treated articles will involve the unprotected general public.
The literature data submitted (6.5(07)/6.7(02) and 6.7 (04-05)) is mainly based on a study by Schmahl and Steinhoff (1960) and a study by Furst, R. and Schlauder, M.C. (1977).
In the study by Schmahl and Steinhoff, subcutaneous injections of colloidal silver resulted in tumours in rats surviving longer than 14 months. Six of the eight tumours found among the 26 rats (23%) were located at the injection site. There were no vehicle controls included in the study but the spontaneous tumour frequency at any site was stated to be 1-3%. Based on this scarce information, it seems as if the frequency of tumours located at other sites was 2/26 (7.7%) and thus above the spontaneous frequency.
In contrast, no fibrosarcomas developed at the injection sites in Fischer 344 rats intramuscularly injected with silver metal powder (Furst and Schlauder). A few cases of mild local inflammation were noted at injection sites but only in the latter stages of the study. At necropsy there were several incidences of encapsulation of the vehicle or injected metal powder but none of the injected legs showed muscular atrophy.
The summary document in 6.5(07)/ 6.7(02) states that local sarcomas have been observed after subcutaneous implantation of silver foil. The document refers to Furst (1979) who states that the relevance of such results for exposure via ingestion is difficult to interpret as they may arise due to a phenomenon called solid state carcinogenesis.
The ATSDR report submitted in 6.2 (08) states that subcutaneous imbedding of silver foil seemed to produce fibrosarcomas earlier and more frequently than several other metal foils. However, the results were only preliminary since the analysis of some of the metals was not complete at the time of publication.
The quality of the original test data cannot be assessed from this second-hand information. Considering the poor quality f other studies in the dossier that were published around the same time (1956), the original publications are not expected to provide further information and they have thus not been requested from the applicant.
Overall, no conclusion with respect to the carcinogenic potential of silver ions can be made based on this data.

3.9.1.2 Comparison with the CLP criteria

Taking into account the considerations presented in the CLP guidance, the results from the study in mice and rats was initially considered to support classification of silver zinc zeolite in category 2 based on the following arguments:

Statistical significance: The differences in tumour incidence at different dose levels are not statistically significant in pairwise comparisons between controls and doses however a positive trend is demonstrated. A statistically significant positive trend, in which all doses are considered, is considered a stronger indication of the biological relevance of an effect compared to a statistically

significant difference at single dose levels. Appropriate statistical methods for assessing differences in toxicological studies are discussed in the OECD guidance "Current approaches in the statistical analysis of ecotoxicological data: A guidance to application", Paragraph 123 states: *"[…] In addition, statistical tests for trend tend to be more powerful than alternative non-trend tests, and should be the preferred tests if they are applicable. Thus, a necessary early step in the analysis of results from a study is to consider each endpoint, decide whether a trend model is appropriate, and then choose the initial statistical test based on that decision. Only after it is concluded trend is not appropriate do specific pairwise comparisons make sense to illuminate sources of variability."* Trend analysis is appropriate for this case as the study includes several dose groups and *"the effect of increasing exposure may show up as an increase or as a decrease in the measured response, but not both."* (paragraph 122).

Background incidence: the rat strain used (F344) is prone to develop mononuclear cell leukaemia and pituitary adenomas. However, this does not necessarily mean that increased incidences of these tumour types should be automatically disregarded. The incidences are higher compared to the concurrent controls and if the substance would act as a promoter an increase of tumours originating from cells that easily become initiated in the test strain used could be expected. A higher tumour incidence occurring in all dose groups and both sexes of (8 observations) by pure chance seems highly unlikely.
Historical control data: Since concurrent controls are sufficient in number and the results for this group does not differ significantly from the results in the low-dose group, there is no reason to let historical control data take precedence over the concurrent control data. Especially taking into account the lack of or limited information on test conditions (e.g. strain, supplier, test facility, housing conditions, diet, group size, administration route, survival rates, assessment criteria etc) in the historical control data presented. Moreover, there are large variations in the historical incidences reported in confidential attachments 1, 3 and 9 meaning that almost any tumourincidence between 4-74% would be covered by such broad range.
in the type of rat strain used and the incidences observed are within the range reported in historical control data.

Human relevance: The type of leukaemia observed is not characterised but even if the tumour type would not be relevant for humans, in case the substance promotes cells into tumours it could yet have the ability to promote cells into the tumour types humans are prone to develop.

Genotoxic potential: The negative result obtained in the comet assay with silver zinc zeolite indicates that the positive findings observed in vitro with silver zinc zeolite (and silver copper zeolite) are not expressed in vivo. However, mutagenicity is a separate hazard class since carcinogenicity is not necessarily linked to this endpoint. As discussed above, silver zinc zeolite could act as a tumour promoter which is a mechanism not linked to genotoxicity

Nevertheless, based on a weight of the evidence analysis of carcinogenicity RAC concluded that data on silver zinc zeolite does not meet criteria for classification.
The opinion was based on the following considerations:
i. the weak statistical significance of the reported incidences in pituitary adenomas without carcinomas
ii. the weak statistical significance of incidences in leukaemia in a very susceptible strain of rats and the absence of leukemia in mice;

iii. the similar cumulative survival rate and the mean survival time in rats and mice;
iv. the comparable ratio of tumours/animal among control and exposed rats and mice at the termination of the studies;
v. the doubts on the human relevance of the leukaemia reported in rats; and
vi. the apparent sex dependence of the reported tumours.

3.9.1.3 Conclusion on classification and labelling for carcinogenicity

Based on a weight of evidence analysis of carcinogenicity, RAC does not consider silver zinc zeolite to fulfil criteria for classification. Consequently, silver zeolite is not expected to fulfil criteria for classification.

3.10 REPRODUCTIVE TOXICITY

3.10.1 Developmental toxicity

Summary table of animal studies on adverse effects on development						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance Dose levels, Duration of exposure**	**NOAELs, LOAELs** *(also for maternal effects)*	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
OECD TG 414* Oral (gavage) Reliability 1-2	Rat SpragueDawley F/30	Silver copper zeolite (3.4% Ag and 6.1% Zn) 200, 700, 2000 mg/kg bw/day Gd 6-15	NOAEL maternal tox: 700 mg/kg bw/day NOAEL embryotox: >2000 mg/kg bw/day	<u>2000 mg/kg bw:</u> ↑death (1/20) ↓body weight (13%) ↓bodyweight gain (25%) ↑clinical signs: sedation, void faeces, urogenital discharge, thinness <u>Foetuses :</u> No effects observed	Read across	Doc IIIA 6.8.1(02)

Summary table of human data on adverse effects on development				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
According to the summary prepared by the Agency for Toxic Substances and Disease Registry it is not known whether silver causes developmental toxicity in humans. There were no studies found regarding developmental effects in humans after exposure to silver but the document refers to a study by Robkin et al. (1973) in which the possibility of a relationship between the concentration of silver in foetal tissues and the occurrence of developmental abnormalities was investigated. The authors reported that the concentration of silver in the foetal liver of 12 anencephalic human foetuses was higher (0.75±0.15 mg/kg) than the values from 12 foetuses obtained either through therapeutic abortions (0.23±0.05 mg/kg), or in 14 spontaneously aborted foetuses (0.21±0.05 mg/kg).The concentration in 9 premature infants was 0.68±0.22 mg/kg. **The authors could not determine if the higher concentration of silver in anencephalic foetuses were associated with the malformation, or with foetal age.**				Doc IIIA 6.2(08)

There is no substance-specific information available for silver zeolite. The applicant considers read-across to data obtained with silver sodium hydrogen zirconium phosphate relevant:
"With regard to reproductive toxicity, silver zeolite is a less complex substance compared to silver zinc zeolite, because of the absence of zinc. A prediction of the likelihood of silver zeolite being toxic for reproduction can be made with reference to existing data for silver sodium hydrogen zirconium phosphate. The information was submitted in the dossier to support the review of silver zinc zeolite. The submitted data were evaluated and concluded in the draft CAR for silver zinc zeolite (May 2012 and January 2015) and in the human health section of the preliminary draft CAR for sodium hydrogen zirconium phosphate, issued in January 2015. Read across is relevant because silver sodium hydrogen zirconium phosphate has high silver availability compared to silver zeolite and both substances contain silver as the only component with the potential for reproductive effects."
This justification is not fully supported. The type of read-across approach used in this assessment is to consider the toxicity of each individual constituent of silver zeolite and to estimate the NOAEL for the substance based on the most conservative data. This is expected to compensate for the inherent uncertainty of the approach. Therefore, it is considered appropriate to use data on silver zinc zeolite to fill the data gap for silver zeolite. The two substances are chemically similar with respect to the zeolite structure and silver ions. Silver zinc zeolite also contains zinc but there is no data demonstrating that the effects of silver zinc zeolite are caused by zinc and thus of less relevance for silver zeolite. According to the RAC opinion[16], silver zinc zeolite meets criteria for classification Repr. 2; H361d. For completeness, all data available and considered relevant for this endpoint is discussed below.

[16] Committee for Risk Assessment (adopted 4 December, 2015), CLH-O-0000001412-86-90/F

The only developmental study availale for the silver zeolites reviewed under BPR (i.e. silver zeolite, silver zinc zeolite and silver copper zeolite) is a study performed with an unspecified type of silver copper zeolite assumed to be AgION Antimicrobial Type AC.
The test substance was administered to rats in daily dietary doses of 200, 700, 2000 mg/kg bw during days 6-15 of gestation.
Two animals in the mid dose group and two animals in the high dose groups were found dead prior to termination. Three of these deaths were attributed to dosing accidents but the death of one high dose dam was considered related to treatment. This female showed hemorrhage from the urogenital tract, dark red kidneys and the stomach was distended with gas and test substance.
The maternal bodyweight and bodyweight gain was approximately 13 and 24% lower at termination in high dose animals compared to controls. Clinical observations considered related to treatment included incidences of wheezing (0/30, 2/30, 6/30 and 8/30 in control, low, mid and high dose groups respectively) and incidences of sedation (11/30), voiding watery faeces (3/30), urogenital discharge (3/30) and thinness (2/30) in the high dose group only.
There were no treatment-related effects in litter parameters except for a difference in sex ratio in treated groups (M/F 49.4/50.6, 53.0/47.0 and 54.0/46.1 in low, mid and high dose respectively) compared to controls (M/F 40.8/59.2). This change was not statistically significant thus the toxicological significance is unclear.
A few abnormalities were noted during the histopathological examinations, but only in single animals from the low and mid dose group and were thus considered incidental. There were no statistically significant differences with respect to the incidence of delayed ossification however no statistical analyses could be made for the phalanges of bones due to processing accidents and incomplete staining. According to the study report, skeletal abnormalities such as wavy ribs, misshapen radii, ulnae and femurs were observed in three foetuses from the same litter (3/223 foetuses examined) of a high dose female. Since individual data for the different types of delayed ossifications is lacking, this information cannot be confirmed. However, according to individual bodyweight data for dams the parent of this litter lost 19 g during the treatment period (day 6-17) and the overall weight gain was only 2 g (mean bodyweight gain in controls was 109 g). The effects are thus likely to be secondary to maternal toxicity.
Besides observations of pale liver and kidney in two high dose females and enlarged spleen in one female of each mid and high dose group, there were no other gross abnormalities reported.
The NOAEL for maternal toxicity is set at 700 mg kg bw based on a reduced bodyweight gain and an increased incidence of clinical signs at 2000 mg/kg bw (LOAEL). In the absence of effects at the top dose, the NOAEL for pup/embryotoxicity/teratogenicity of silver copper zeolite is considered to be higher than 2000 mg/kg bw.

Developmental toxicity of other silver containing active substances:

Silver sodium hydrogen zirconium phosphate: The developmental toxicity of the substance was tested first in a preliminary oral gavage study in eight rats and then in a standard developmental toxicity test with 25 Sprague-Dawley rats. In both studies animals were administered 0, 100, 300 and 1000 mg/kg bw during days 6-15 of gestation. All animals survived through the main study except for a mid-dose dam who was killed in extremis with signs of respiratory distress that were considered to be the result of a dosing trauma. There were no clinical signs observed in the studies and no significant effects on food consumption or bodyweights. The pregnancy index, implantation data and live litter size parameters were similar between treated animals and controls. The only difference noted was a dose related increased of the percentage males per litter which was statistically significant in the high dose group (56.8% compared to 43% in controls). The significance of this finding is unclear since the opposite pattern was observed in

the preliminary study (40.3% in high dose and 50.6% in controls) but an increased percentage of male foetuses was also observed in the study with silver copper zeolite. There were no differences among foetal parameters such as litter weight data, visceral/skeletal malformations or variations. The NOAEL and LOAEL for maternal/pup embryotoxicity/teratogenicity was higher than 1000 mg/kg bw based on the absence of toxicity at the highest dose tested. Based on data obtained in the release study, this corresponds to a NOAEL above 25 mg silver ion equivalents/kg bw.

Literature data; silver chloride (Doc IIIA, 6.8.1(03): In a published study by Shavlovski et al., a dose of 50 mg silver chloride /animal (less than approximately 250 mg/kg bw/day) was administered in diet to 20 inbred albino female rats from the first day of the study to termination (day 20). A group of five rats was also used to study the effect of silver during the period of organogenesis (days 7-15 only). The study also investigated effects in untreated control rats, in rats administered injections of human ceruloplasmin and rats administered bipyridyl or penicillin (Cu/Fe chelators).
The results show that if dams were exposed between days 1-20, the incidence of post-implantation deaths (36%) increased compared to control (9.6%) and historical controls (8.7%) and all newborn animals died within 24 hours. Moreover, the incidences of hydronephrosis (31%) and cryptorchidism (35%) increased substantially compared to controls (5.3 and 1.3% for hydronephrosis and cryptorchidism respectively) and historical controls (1.2 and 0.8% respectively).
The survival of newborns was improved if injections of human ceruloplasmin were received during days 2-14 and survival was almost comparable to controls if CP injections were received during days 8-21. The deaths of embryos and newborns were explained as a consequence of copper deficiency caused by silver inhibiting copper from binding to the transportprotein ceruloplasmin. This theory was supported by the increased survival (and reduced frequency of teratogenic effects) in AgCl treated rats who received injections of human ceruloplasmin as well as by the lack of copper in placenta, embryos and blood serum of adult rats treated with AgCl. In addition, malformations were exacerbated when chelator bipyridyl was co-administered. There were no effects in rats treated with AgCl during organogenesis only and this was considered to be due to active ceruloplasmin gradually decreasing from blood.
Although the study was not performed according to GLP or a recognised guideline, the result is considered reliable since the publication has been peer-reviewed and the experiment seems to be well conducted. Several parameters requested in OECD TG 414 were not investigated but the study yet raises serious concern for developmental toxicity of silver, especially since the author states that the treatment did not alter the physiological functions of the dams. Since effects were noted at the only dose level tested, no NOAEL for teratogenic effects can be set in this study.

Literature data; silver acetate (Doc IIIA, 6.8.1(07): In a published NTP study prepared for National Toxicology Program, the effects of silver acetate on CD albino rats during days 6-19 of gestation was investigated at doses of 10, 30, or 100 mg/kg/day. All animals survived treatment except for a high dose dam exhibiting signs of morbidity and a high dose dam excluded due to a misdirected dose. Clinical signs such as piloerection and minor bodyweight changes were noted in all animals and other signs indicative of toxicity such as alopecia and rooting after dosing were observed in high dose animals. There were no significant effects on maternal body weight gain, food or water consumption during pre-treatment, treatment and gestation period. The number of pregnant dams was reduced in high dose dams (87.5% compared to 96%) but the difference was not statistically significant and did not show a

dose-response. Other reproductive parameters did not differ from controls. The percentage litters with late foetal deaths was increased in the high dose group (incidences: 0/24, 0/23, 0/25 and 2/20) resulting in a statistically significant positive trend in the Cochran-Armitage test. The incidence was above historical control data (0-4.35%) but the study authors did not regard the result of this study as clear evidence of prenatal mortality since the number of late fetal deaths/litter was not affected by treatment (it is noted though, that although not statistically significant, the percentage late fetal deaths /litter was 1.22 in high dose group compared to none in control and the lower dose groups). A negative trend that was statistically significant was observed for average male foetal bodyweight/litter and percent litters with late foetal deaths (Cochran-Armitage test) in test for linear trend. The incidence of malformations (external, visceral, skeletal) waslower in the high dose group compared to the control. The number of skeletal variations/litter and the percentage of litters with any variation was increased in high dose animals compared to controls. The skeletal variations included unossified sternebrae, rudimentary rib, short rib, bipartite ossification center. Considering that there wasno dose-response and that the difference was not statistically significant, the observation is not given further toxicological significance.
The NOAEL set for maternal toxicity was 30 mg/kg bw based on clinical signs of toxicity and the NOAEL for pups was 30 mg/kg bw based on the decreased average male foetal bodyweight/litter and average total foetal bodyweight/litter at 100 mg/kg bw (LOAEL). The NOAEL for embryotoxicity/teratogenicity is 30 mg/kg bw based on the increased incidence of the percent litters with late foetal deaths in the high dose group. Based on a silver content of 64.6% and the assumption that silver acetate is completely dissolved in the stomach, this would correspond to a NOAEL of 19.4 mg silver ion equivalents/kg bw.

Literature data, silver acetate: The reproductive toxicity of silver acetate was further investigated in a recent rat one-generation study published in 2016. To mimic the most likely human exposure route, silver acetate was administered in the drinking water at dose levels of 0, 0.4, 4 and 40 mg/kg bw/d, equivalent to approximately 0, 0.25, 2.5 and 25 mg/kg bw/d silver. Groups of (P) rats (20/sex) were administered the test material throughout a 10-week pre-mating period and during mating. Females continued to be exposed during gestation and lactation; males were terminated following exposure for 90 days. The resulting (F) litters were culled (5/sex where possible) on PND4 and offspring were further selected following weaning on PND21 (1/sex/litter) and remained untreated until termination on PND26. Parental animals were observed for clinical signs; bodyweights, food and water consumption were measured periodically. Gross necropsy was performed on all parental animals; weights of selected organs were measured and histopathological examinations were made for a limited selection of tissues and the testes of 10 males/group were additionally assessed using specific staining following perfusion fixation. The major deviations in the study include the lack of GLP compliance, lack of individual animal data and the lack of further investigations of important parameters such as oestrus cycle, sperm parameters and histopathological analyses of reproductive tissues. Nevertheless, the study is claimed to follow the current protocols for testing foods and food additives (FDA CFSAN Redbook, 2000) and overall, the study seems to be of good quality and results are considered reliable.
Only a few effects were noted in parental animals including a reduced fluid consumption that reached statistical significance on some occasions, reduced stomach weights and pigmentation of organs and tissues. The severity of pigmentation was dose-related and occurred in all treated animals thus a parental NOAEL cannot be set.
However, severe effects were noted with respect to fertility index and fetal/pup viability:

• reduced fertility and numbers of litters and implants and reduced male pup survival in the 40 mg/kg dose group;
• a reduction in pup body weight and an increase in the numbers of runts in the 4.0 mg/kg dose group;
• a reduction in female pup weight and male pup weight at PN day 26 in the 4.0 mg/kg and 40 mg/kg dose groups, respectively
The reason why the higher and statistically significant number of runts in the 4.0 mg/kg group was not as clearly observed in the 40 group mg/kg dose may be the fetal/pup mortality in the high dose group masking such effects.

	M				**F**			
	0	**0.4**	**4**	**40**	**0**	**0.4**	**4**	**40**
No. exposed to mating	19	20	20	20	20	20	20	20
No. (produced) plug or sperm-positive females	17	19	19	18	20	20	20	20
Mating index	89.5	95.0	95.0	90.0	100.0	100.0	100.0	100.0
Fertility index 1 (no prod litter/no prod plugs/sperm-positive) ×100	100.0	100.0	100.0	**88.9**	100.0	100.0	100.0	**80.0**
Fertility index 2 (no prod litter/no prod plugs/sperm-positive) ×100	89.5	95.0	95.0	**80.0**	100.0	100.0	100.0	**80.0**
Producing litters (#)	17	17	19	16	20	20	20	**16**
With implantations (#)					20	20	20	**18**
Total resorption (#)					-	-	-	**2**
Litters (#)					20	20	20	**16**
Total litter loss (#)					1	1	1	2
Non-viable pups only (#)					-	-	1	-
Viable litters (#)					19	19	18	**14**
Implantations (#)					14.4	14.0	14.3	**11.3***
Litter size (#)					13.1	12.4	13.4	**10.3***
Live pups (#)					13.0	12.3	12.8	**10.5[a]**
*significantly different to controls (p≤0.05); a (p≤0)								

The effects noted in this study are consistent with effects noted in the study with silver chloride and the developmental effects observed in a two-generation study with silver zinc zeolite. This is further discussed in section 3.10.4.

Literature data; silver lactate: Rungby and Danscher (1983) have demonstrated silver in the brains of neonatal rats exposed *in utero* when dams received intraperitoneal injections of silver lactate on days 18 and 19 of gestation. This observation indicates an intrinsic ability of to pass the blood brain barrier (6.8.1(04)).

The significance of the information available for different SCAS on the overall assessment of fertility effects of silver zeolite is discussed in section 10.4.

Conclusion used in Risk Assessment – Effects on development	
Value/conclusion	Please refer to section 3.10.4
Justification for the value/conclusion	Please refer to section 3.10.4

Data waiving	
Information requirement	There is no developmental toxicity data for the second and most sensitive species. However, no further information is required since developmental toxicity effects of silver substances are not expected to be detected in a developmental toxicity study with exposures limited to the period of gestation. Since ceruloplasmin is a key enzyme also in rabbits, the proposed MoA (i.e. silver replacing copper in ceruloplasmin) can be expected to occur also in this species (see section 3.10.4). Although it cannot be excluded that there may be an additional MoA for developmental toxicity of silver ions in rabbits this uncertainty is not considered to justify further animal testing. There are no developmental toxicity studies in rabbits for any of the SCAS.
Justification	See section 3.10.4

3.10.2 Fertility

Summary table of animal studies on adverse effects on fertility						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance Dose levels, Duration of exposure**	**NOAELs, LOAELs**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
OECD 416 Oral in diet Reliability 1	Rat SpragueDawley Crl: CD® IGS BR 28/sex	Silver sodium hydrogen zirconium phosphate Exp.add 9823-37 (10% Ag)	NOAEL/LOAEL Parental F0: 1000/5000 Parental F1: 1000/5000	**Parental:** F0 20 000ppm: ↑pigmentation (pancreas)	Read across	IIIA 6.8.2-03 (2002)

		1000, 5000 and 20000 ppm corresponding to 72.5/78.2, 363/400 and 1465/1612 mg a.s/kg bw in F0 males and females (premating) approximately 1.9, 9.9 and 40 mg silver ion equivalents/kg bw/d in females) Maturation, mating, gestation and lactation for two successive generations	Offspring F1:1000/5000 Offspring F2: 1000/5000 Reproduction: 5000/20 000	↓ thymus weight (20% m), seminal vesicle/coagulating gland (14%), adrenals (14%), kidneys (m, 16%) ↑spleen weight (m, 11%), rel brain weight (m, 9.7%) <u>F0 5000ppm:</u> ↑pigmentation (pancreas) ↑spleen weight (m, 20%) ↓seminal vesicle/coagulating gland (14%) <u>F1 20 000:</u> ↑mortality (4m, 2f, none in control) ↓bodyweight pairing (≤ 16%), gestation (≤ 10%) lactation (≤ 10%) ↓food consumption pairing (≤ 20), m), gestation, lactation (≤22%) ↓number born (11%) ↑pigmentation (pancreas, lymph nodes, thymus) ↓uterus (abs/rel 28/23%), prostate (abs/rel 33/25%) ↑relative epididymis weight (left/right 9.6/19%) <u>F1 5000 ppm:</u> ↑pigmentation (pancreas, lymph nodes, thymus) Offspring: <u>F1 20 000:</u> ↓ group mean litter weights (8%, day 21), group mean individual weights (9%, day 21)		

				thymus weight (m/f 38/32%) <u>F1 5000 ppm:</u> ↓ thymus weight (m 22%) <u>F2 20 000:</u> ↓ group mean litter weights (13%, day 1), group mean individual weights (13%, day 21) ↓ thymus weight (m/f 38/37%) ↓live litter size (13%, day 1) <u>F2 5000:</u> ↓ thymus weight (f 19%) Reproduction: F2 20 000: ↓ number born (11%) ↓live litter size (13%, day 1)		
OECD 416 Reliability 2	Rat Sprague Dawley Crl: CD® (SD) IGS BR 30/sex	AgION Silver Antimicrobial Type AK Oral in diet m/f: 72/87, 472/548, 984/1109 mg/kg bw (premating) This corresponds to approximately 1.5/1.8, 9.8/11.3; and 20.3/22.9 mg silver ion equivalents/kg bw/d in males and females Maturation, mating, gestation and lactation for two		**Parental:** **<u>F0</u>** <u>12500:</u> ↑ Mortality (m 10%) ↓Bodyweight (m≤10% (pre/post pairing, f 6% gestation day 20, ≤ 11%) ↓Bodyweight gain (m≤17% (pre pairing), f gestation 14-20:29% 0-20:16%) ↓Food consumption (premating m ≤8%, lactation 0-4:27%, 4-7: 12%, 7-14: 21%, 14-21: 27%) ↑RBC (m/f 13/15%), platelets (m/f 42/45) ↓Hb (m/f 16/12%), HCT (m 9%)	Read across	

		successive genera-tions		MCH (m/f 25/23%) MCHC (m/f 7/6%), ↑Pigmentation of organs ↑Histopathological changes in kidneys (including hydronephrosis (8m/2f , 3m in controls) , urinary tract ↓ kidney weight (m abs/rel 14/3%, f rel brain 7%) rel brain weight (m, 9%) ↑ epididymis left/right (rel bw 11/9%) Spleen (m, 7%) Testis (rel left/right 12/10%) <u>F0 6250:</u> ↑ Mortality (m, 3.3%) ↑RBC (f 11%), ↓ MCV (m/f, 6/9%), MCH (m/f 6/12%), MCHC (f, 3%) ↑Pigmentation of organs ↑Histopathological changes in kidneys (including hydronephrosis 7m/2f, 3m in controls)) ↓kidney weight (m, abs/rel bw 13/7%) spleen (m, abs/rel bw 14/21%) <u>F0: 1000:</u> ↑Pigmentation of organs **<u>F1</u>** <u>12500:</u> ↑Mortality (m/f 93.3/76.7%) ↓Bodyweight (premating m/f ≤ 56/46%) ↓Bodyweight gain (premating m/f ≤ 47/40%) ↑Histopathological changes		

				↑Thymus atrophy <u>F1:6250:</u> ↑Mortality (m/f 23.3/3.3%) ↓Bodyweight (premating w1-10 m/f 25-13/19-2 (n.s.s)%, post-pairing m ≤12%, gestation n.s.s, lactation≤ 10%) ↑Histopathological changes (including hydronephrosis 10 m/4f , 0 in controls) ↑Kidney weight (m/f, abs 19/11%, rel bw 9/8%, rel brain 13/7%) ↓Brain (m/f, 7/5%) Adrenal (m, abs 18%, rel brain 12%) epididymis left/right (abs 14/11%, rel brain (left 9%)) Spleen (m, rel bw 11%) Testis (abs left/rel brain right 12/7%) Prostate (rel brain 13%) Seminal vesicle (8%) Liver (f, 8%) ↑Thymus atrophy (thymus not weighed in F1 adults) F1 1000: ↑Mortality (m 3.3%) ↑Pigmentation of organs ↑ Hydronephrosis (3m, 1f, 0 in controls) **Offspring:**		

				F1 12500: ↓total pups born/litter (15%) ↑stillborn index ↓livebirth index ↓liveborn/litter (27%) ↓pup survival indices (Days 0-4 precull 46% (45% day 4 pre-culling then ≤29%)) ↑clinical signs ↓body weights M+f Day 0: 15% Day 4:pre/post culling: 19% Day 7: 23% Day 14: 26% Day 21: 36% Day 26: 47% ↓organ weights Brain 18% (rel bw ↑58%) Spleen 26% (rel bw ↑31%) Thymus (m/f abs 74/70%, rel bw 53/47%, rel brain 69/64%) ↓sex ratio ↑day of vaginal opening (day 59.9, control: 35.1) and preputial separation (day 56.7, control: day 44.5) ↑histopathological changes F1 6250: ↑clinical signs ↓ body weights M+f Day 14: 13% Day 21: 25% Day 26: 47% ↓organ weights Brain 10%, rel bw ↑27%		

				Thymus (m/f abs 58/55%, rel bw 39/39%, rel brain 53/51%) ↑Spleen (m/f rel bw 31/32%) ↑day of vaginal opening (day 39.8) and preputial separation (day 47.4) ↑histopathological changes <u>F1 1000:</u> ↓organ weights Thymus (m abs 13%, m/f rel bw 10/9%, m rel brain 11%) **F2** 6250: ↑stillborn index ↓livebirth index ↓bodyweights Day 0: 5% Day 4: pre/post culling: 12% Day 7: 15% Day 14: 18% Day 21: 20% ↑histopathological changes ↓organ weights Brain (m/f 10/7%, rel bw ↑21/25%) Thymus (m/f abs 50/54%, rel bw 37/42%, rel brain 47/50%) Spleen (m abs 18%) <u>F2 1000:</u> ↓Thymus weight (m rel bw 11%) Reproduction: ↑stillborn index (F1, F2) ↓livebirth index (F1, F2)		

				↑day of vaginal opening and preputial separation		
The study was performed according to the current protocols for testing foods and food additives (FDA CFSAN Redbook, 2000). Reliability 2	Sprague-Dawley [Crl:CD®(SD) IGS BR] 20/sex	Silver acetate KSCN %Ag: 63.7-65.5% 0, 0.4, 4.0 and 40.0 mg/kg bw/d approximately 0, 0.25, 2.5 and 25 Ag+ mg/kg bw/d.	Parental/Repr: 4.0/40 Dev: 0.4/4.0	**Parental:** 40 mg/kg bw/d Organ weights (f): ↓ stomach (40%) ↓ liver (9%) ↓ Feed consumption (16%) until lactation day 18 (f) **Reproduction** <u>40 mg/kg bw</u> <u>Fertility index</u> ↓ 20% (not stat analysed) Implantations ↓ 22% (11.3 compared to 14.4 in control) Fertility **Development** 40 mg/kg bw/d: ↓litter size (21%) (10.3 compared to 13.1 in control) ↓live pups (19%) (10.5 compared to 13.0 in control)) F1 pups (40 mg/kg): reduced male pup survival ↓pup survival (m) ↓pup weight PN day 26 (m): 8% <u>4.0 mg/kg</u> ↓pup weight PN day 26 (f): 12% ↑numbers of runts	Read across The main deficiencies of this study include the lack of GLP compliance, lack of individual animal data and the lack of further investigations such as oestrus cycle, sperm parameters and histopathological analyses of reproductive tissues (Histopatholog-	IIIA 6.8.2-06

				(Day 4 pre-cull: 35 tot/9 of 18 litters compared to 11 tot/7 of 19 in control) (Day 4 post-cull: 27 tot/8 of 18 litters compared to 7 tot in 4 of 19 in control) (Day 7: 25 tot in 10 of 18 litters compared to 7 tot in 4 of 19 in control)	ical examinations of vagina, uterus and ovaries)	

Summary table of human data on adverse effects on fertility				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available.				

Conclusion used in Risk Assessment – Fertility	
Value/conclusion	Silver zeolite is not expected to cause adverse fertility effects.
Justification for the value/conclusion	The conclusion is based on data obtained with silver zinc zeolite AgION Antimicrobial Type AK .

Data waiving	
Information requirement	Fertility effects of silver zeolite has not been investigated in a multigeneration study however no further information is required to assess this endpoint.
Justification	See discussion in section 10.4.

There is no substance-specific study investigating effects of silver zeolite.
The applicant considers waiving of this study justified on the following basis: *"With regard to reproductive toxicity, silver zeolite is a less complex substance compared to silver zinc zeolite, because of the absence of zinc. A prediction of the likelihood of silver zeolite being toxic for reproduction can be made with reference to existing data for silver sodium hydrogen zirconium phosphate. The information was submitted in the dossier to support the review of silver zinc zeolite. The submitted data were evaluated and concluded in the draft CAR for silver zinc zeolite (May 2012 and January 2015) and in the human health section of the preliminary draft*

CAR for sodium hydrogen zirconium phosphate, issued in January 2015. Read across is relevant because silver sodium hydrogen zirconium phosphate has high silver availability compared to silver zeolite and both substances contain silver as the only component with the potential for reproductive effects."
As previously stated (section 3.10.1) this proposal is not supported as the zeolite part also needs to be addressed. According to the RAC opinion , silver zinc zeolite meets criteria for classification Repr. 2; H361d (see below). Published results from studies with silver acetate and silver chloride show similar effects as those seen with silver zinc zeolite. Therefore, data on silver zinc zeolite cannot be dismissed solely based on the presence of zinc. Consequently all data must be considered in a weight of evidence approach.
The dossier contains two different fertility studies (two-generation studies) performed with silver sodium hydrogen zirconium phosphate and silver zinc zeolite, respectively. In addition, a recent fertility study performed with silver acetate is available in the open literature (see section 3.10.1).

Results with silver sodium hydrogen zirconium phosphate:
Silver sodium hydrogen zirconium phosphate in the form of Exp.add 9823-37 (also known as AlphaSan® RC2000) was tested in rats in a study perfiormed in accordance with OECD guideline 416. The test substance was administered in dietary doses of 1000, 5000 and 20000 ppm to two generations of rats throughout maturation, mating, gestation and lactation.
Parents F0: There were no treatment related deaths in the F0 generation and no effects on bodyweights, food consumption, reproductive parameters or litter parameters (litter size and viability).
Increased relative weight of spleen and decreased absolute weight of seminal vesicles/coagulating gland was observed in high and mid dose males whereas a decreased absolute weight of thymus was observed in high dose males only. The pathological examinations showed pigmentation of pancreas in high and mid dose males and females.
Parents F1: Four high dose males and two high dose females died in the FI generation whereas all F1 control animals survived. One animal was killed due to suspected dystocia and pathological findings were observed in the stomach of two animals. For the remaining animals, the cause of death was unclear.
The bodyweights of male rats were reduced the entire period before pairing and the bodyweights of female rats were reduced during the first three weeks before pairing and during the entire gestation and lactation periods. Food consumption was reduced in males during the last weeks of maturation and during the first days of gestation and lactation in females (≤ 10%).
There were no effects on reproductive parameters with the exception of the pre-coital interval which was longer in high dose females compared to controls. Since this did not affect fertility, it is not given further significance. The parturition index was lower in high dose females (90.9%) than in controls (95.4%) but the change was neither dose-related nor statistically significant in chi square analysis. There were no effects on live birth index or the viability index but the number born and the litter size at day 1 was reduced in high dose females compared to controls.
The absolute weights of adrenals, kidneys, seminal vesicles/coagulating gland and right testis were reduced in high dose males and the relative brain weight, epididymides was increased in this group. The absolute and relative prostate weight was reduced more than 25% in high dose males. A dose-related decrease in prostate weight was also observed in F0 males but statistical significance was not achieved. The only statistically significant change observed among organ weights in females was a reduced absolute/relative weight of uterus (28/13%) in the high dose group.

Pigmentation of pancreas, lymph nodes and thymus was observed in high and mid dose animals.
According to the study author, there were no significant differences in the proportions of each of the follicle however the total number of follicles (small, medium and large) was lower in high dose animals (7.7/7.5/5.6 in (ovary 1/ ovary 2/ overall respectively) compared to controls (10.4/10.1/10.2 respectively). Since there were no effects on reproductive performance, this observation is not given further significance.
F1 pups: The litter weights and the mean individual weights were reduced by 8 and 9% at the end of lactation (day 21). There were no effects on landmarks of development (pinna unfolding, tooth eruption and eye opening) or on reflexological responses (surface righting reflex, mid-air righting reflex, startle reflex, pupillary reflex). The weight of thymus was reduced in both male and femal mid and high dose pups.
The pathological examination showed pigmentation of pancreas and the mesenteric lymph nodes in high and mid dose males and females.
F2 pups: The litter weights were reduced by 13% at day 1 of lactation and the mean individual weights were reduced by 13% at the end of lactation (day 21). There were no effects on landmarks of development (pinna unfolding, tooth eruption and eye opening) or on reflexological responses (surface righting reflex, mid-air righting reflex, startle reflex, pupillary reflex).
The weight of thymus was reduced in both male and female mid and high dose pups. Pigmentation of pancreas and the mesenteric lymph nodes was observed in high and mid dose males and females. The frequency of increased renal pelvic cavitation seemed to be slightly higher in high dose males (6) than in controls (1).
The NOAEL for parents was considered to be 1000 ppm based on organ pigmentation (pancreas, mesenteric lymph nodes in both sexes and generations) and organ weight changes in F0, F1 parents. Based on the lowest reported test substance intake during premating, this corresponds to 72.5 mg/kg bw (F0 males, 1.9 mg silver ion equivalents/kg bw/d). Using a back-calculation of the chronic NOAEL set for pigmentation, **a $NOAEL_{offspring}$ of 136 mg/kg bw/d can be estimated for silver zeolite.**
The NOAEL for offspring was 1000 ppm based on the reduced thymus weight in high dose F1 and F2 pups and in male mid dose F1 pups. Based on the lowest reported test substance intake in females during premating, this corresponds to 78 mg/kg bw (1.9 mg silver ion equivalents/kg bw/d) (F0). Using a back-calculation of the chronic NOAEL set for pigmentation, **a $NOAEL_{offspring}$ of 136 mg/kg bw/d can be estimated for silver zeolite.**
The NOAEL for reproduction was 5000 ppm based on a reduced number born in high dose F1 animals and reduced live litter size (day 1) in high dose F2 animals. Based on the lowest reported test substance intake in females during premating (test substance intake is only available for premating period), this corresponds to 400 mg/kg bw (9.9 mg silver ion equivalents/kg bw/d) (F0). Using a back-calculation of the chronic NOAEL set for pigmentation, **a $NOAEL_{reproduction}$ of 707 mg/kg bw/d can be estimated for silver zeolite.**

Results with silver zinc zeolite: In a two-generation reproduction and fertility study in rats, the silver zinc zeolite denoted AgION Silver Antimicrobial Type AK was administered through the maturation, mating, gestation and lactation periods for two successive generations.

Parents F0: Three males administered the high dose and one male administered the mid dose died during the study. The cause of death could not be established but the deaths were considered related to treatment by the study author. Bodyweight and body-weight gains were reduced in males during premating by ≤ 10 and 17% respectively. After mating, the male bodyweight gain was comparable for all groups.
One female control animal died during the study but no deaths occurred among the treated F0 females. The bodyweights were reduced in high dose females at day 20 of gestation and at day 7, 14 and 21 of lactation but did not fall below 11% of the bodyweight in controls. The bodyweight gain was reduced during gestation, during days 0-20 by 16% and days 14-20 by 29%. The bodyweight gain during lactation was at some of the measurements significantly increased or decreased compared to controls, but the overall bodyweight gain during lactation (days 0-26) was not statistically significantly different from controls.
Food consumption was reduced between 12 and 27% in the high dose group during lactation and the changes were statistically significant. The reduced bodyweight gain and food intake is further discussed in section 4.11.5.
High dose males and females had increased levels of erythrocytes, platelets and decreased levels of hemoglobin (Hb), hematocrit (HCT), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). Some of these parameters were also slightly affected in mid dose males and females. The same effects were seen also in the repeated dose studies performed with silver zinc zeolite Type AK and were considered to be caused by zinc. According to the repeated dose study report, zinc prevents uptake of copper in the GI tract which suppresses production of ceruloplasmin. This in turn leads to decreased iron transport and decreased synthesis of hemoglobin.
There were no clinical signs observed and no effects on reproductive parameters that were statistically significant.
Pigmentation was observed in several tissues of mid and high dose animals and mild pigmentation of pancreas and thymus was observed also in some females of the low dose group. Histopathological changes in the kidneys (including hydronephrosis) were noted in high and mid dose animals. Kidney weights were decreased in high dose male and females. The thymus was not weighed.
The gestation length was slightly increased (22.3 compared to 21.9 days in controls) in treated animals and the change was statistically significant for the mid and high dose group. Adverse effects on reproduction was manifested in high dose animals as reduced mean number of live and total pups at birth, reduced live birth index, increased number of stillborn pups and increased stillborn index (see tables 25 and 27). Complete pup mortality was observed in six females of the high dose group. Since the number of corpora lutea was not recorded in the animals, it is not possible to establish if the reduced total number of pups born were due to pre or post-implantation losses.
Parents F1: The mortality in the high dose (12500 ppm) animals was considerable and 28/30 males and 23/30 females died prior to the end of the premating period. The group was therefore terminated after this phase and there were, consequently no pups from this group. The cause of death was not clearly established but discoloration of organs, histopathological changes in the kidneys, decreased size of thymus, enlarged heart and spleen, penile distention/extension and red discoloration were noted among the dead animals.
Body weights of F1 males administered 6250 or 12500 ppm were lower than controls at the start of and throughout the premating, pairing and post-pairing periods and until termination of the high dose group. The body weight gain in males administered 6250 ppm was however comparable to controls over the entire premating period. Bodyweights of mid dose F1 females were statistically lower during the first six weeks of premating and also at one timepoint during lactation but there were no statistically significant

effects on body weight gains during overall (week 1-12) premating, gestation or lactation. Food consumption was reduced in high dose animals and in mid dose males during the entire study.
The macroscopic examinations of F1 animals revealed changes in the urinary tract and in the kidneys. Effects on kidneys included mild caliculi, mild to moderate pelvic dilation and an increased incidence of mild to moderate cortical surface irregularity. Most often cortical surface irregularity corresponded to microscopical changes such as chronic interstitial nephritis and/or infarction. In addition, two males administered 6250 ppm had mild calculus formation in the urinary bladder. Low and mid dose animals had an increased frequency of hydronephrosis (increased frequency compared to P0) Tan/brown discoloration of multiple organs were observed in animals (pancreas, thymus, glandular stomach, duodenum, jejunum, mandibular salivary glands, Harderian glands, exorbital lacrimal glands, pineal gland and urinary bladder. A low incidence of thymic athrophy was noted in animals administered 1000 (premating 71/87 mg/kg bw/d in males and females respectively)) or 6250 ppm (m/f: 477/582 mg/kg bw/d).
Organ weight analysis of animals administered 6250 ppm showed an increased relative weight of spleen (only significant in males), reduced absolute brain weight in males and females, reduced absolute/relative weight of prostate, reduced absolute weight of seminal vesicle, reduced absolute/relative weight of both testes and reduced absolute weight of uterus/oviducts/cervix. Reduced kidney weights were observed in males and females administered 1000 or 6250 ppm. Other statistically significant changes observed were not considered related to treatment. Splenomegaly correlated microscopically with increased extramedullary hematopoiesis and is assumed to be related to treatment since anemia was observed in the F0 parents.
There were no statistically significant or clearly dose-related effects on the fertility parameters. It is noted however that the percentage of abnormal sperm was higher in treated animals compared to controls (0.50 in the mid dose (6250) group, 1.41 in the low dose group and 0.18 in controls). In the absence of statistical significance and effects on fertility, the significance of this finding is unclear.
The percentage of females delivering litters with stillborn pups was increased in the 6250 ppm group and this was also reflected as an increased stillborn index and decreased live birth index.
Offspring, F1 pups: Day 0-4 pup survival was low in the high dose group (53.1% compared to 98.9% in controls) and 5/27 females that delivered litters with live pups failed to retain live pups to Day 4. The male/female sex ratio was reduced at day 0, 4 (pre/post culling), day 21 and 26 but the effect was only statistically significant on day 4 (preculling).
Clinical signs in pups pre-weaning included decreased activity in mid and high dose animals and discoloured skin (blue/pale) and difficult breathing in high dose animals. The discoloration was mainly observed at day26 day whereas decreased activity and breathing difficulties were observed at day 0 or 4. There were no abnormalities detected in the clinical observations of dams made during lactation.
Statistically significant reduced bodyweights were observed at all measurements of male and female pups administered 12500 ppm and at day 14, 21 and 26 in male and female pups administered 6250 ppm.
The absolute weights of brain, spleen and thymus was reduced in pups administered 6250 and 12500 ppm. These changes were statistically significant (except for spleen in 6250 pups). The changes remained statistically significant also when these organ weights (except for the spleen) were related to bodyweights.
A dose-related delay in the day of vaginal opening and preputial separation was observed in all treated animals and the delay was significant in the mid and high dose group. Since the bodyweights were comparable between treated females and controls on the

day of vaginal opening, the delay seems related to the reduced bodyweights. The bodyweights of 6250 and 12500 ppm males were yet reduced by 12,5 and 38% respectively at the time of preputial separation.
There were no treatment related histopathological findings in the stillborn pups or in day 4 culled pups. Changes in the kidney (pale, dilation, cyst) liver (pale) were observed at day 26 in males and females administered 6250 or 12500 ppm. Moreover, cardiac changes were observed in both sexes of high and mid dose animals; mildly enlarged heart in 6/14 males and 6/18 females in 12500 group and 5/27 males and 4/26 females in 6250 group compared to 0 in controls). Small thymus was observed in 2/14 high dose males and 2/18 females.
F2 pups: The number of live pups/litter was decreased in the low dose group at day 4, 14 and 21 due to the complete loss of pups in two litters but there was no effect in the 6250 ppm animals. Pup body weights were lower in 6250 ppm pups than in controls at birth and were further reduced throughout the pre weaning period.
Organ weight analysis showed reduced absolute/relative thymus and brain weights in males and females administered 6250 ppm.
The macroscopic examinations of F2 pups at day 21 (weaning) revealed mild to moderate decreased size of thymus, mild cardiac enlargement, mild renal pallor, mild hepatic pallor and mild pulmonary pallor in animals of the 6250 ppm group.
Analysis of copper, silver and zinc in homogenates of three whole pups from control, 1000 and 6250 pups showed a general decrease of copper in the treated groups whereas the levels of silver and zinc were generally increased (table 25). This analysis does not confirm but supports the mechanism proposed by Shavlovski (see section 4.11.3).

A NOAEL for parents and offspring could not be set since pigmentation of organs were observed in all adults at all dose levels and reduced thymus weights were observed in F1 adults and in F2 pups administered the lowest dose (i.e. 1000 ppm). F1 animals administered 1000 ppm also had an increased incidence of hydronephrosis (see tables 25 and 28).
The LOAEL was at or below 1000 ppm which corresponds to 72/87 mg Type AK/kg bw/d and (based on pre mating values).
The NOAEL for reproduction was 1000 ppm (approximately 70 mg Type AK/mg kg bw and 1.5 mg Ag ion equivalents) based on a decrease in livebirth index, increase in stillborn index, reduced bodyweights in F2 pups administered 6250 ppm (approximately 470 mg Type AK/kg bw/d) and reduced bodyweight gain in F1 pups with a subsequent delay in day of vaginal opening and preputial separation. Using a back-calculation of this NOAEL based on silver content, **a $NOAEL_{reproduction}$ of 107 mg/kg bw/d can be estimated for silver zeolite.**
The same effects although more severe (and accompanied by a reduced pup survival) were observed in F1 pups of dams administered 12500 ppm.

Results with silver acetate:
The effcts noted in the one-generation study include reduced fertility, reduced numbers of litters and implants and reduced male pup survival in the 40 mg/kg dose group; reduced pup body weight and increased number of runts in the 4.0 mg/kg dose group; reduced female and male pup weight at PN day 26 in the 4.0 mg/kg and 40 mg/kg dose groups, respectively (see section 3.10.1). The lack of a statistically significant increase of runts in the high dose group may be explained by the increased fetal/pup mortality masking this effect.
The **offspring NOAEL** is considered to be 0.4 mg silver acetate/kg bw/d based on the increased number of runts in the middle dose. This dose corresponds to 0.25 mg silver/kg bw/d. The dose Type LGK needed to achieve this dose would be 18 mg/kg bw/d.

The **reproductive NOAEL** is 4 mg/kg bw/d (2.5 mg silver/kg bw/d) based on the reduced numbers of litters and implants and reduced male pup survival in the 40 mg/kg dose group. The dose Type LGK needed to achieve this dose would be 178 mg/kg bw/d.

Some weight changes in sex organs were noted for both generations in the studies with silver zinc zeolite as well as silver sodium hydrogen zirconium phosphate. However, there was no clear pattern as the organ weight could be increased in the first generation and decreased in the second and it is not possible to exclude that effects only results from technical difficulties during the dissection process. Although it is not safe to fully exclude that silver may have an endocrine effect, these observations are to weak to justify any further action at this stage.

3.10.3 Effects on or via lactation

Summary table of animal studies on adverse effects on or via lactation						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance Dose levels, Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available						

Summary table of human data on adverse effects on or via lactation				
Type of data/ report	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in Risk Assessment – Effects on or via lactation	
Value/conclusion	Not applicable
Justification for the value/conclusion	No data available

3.10.4 Overall conclusion on reproductive toxicity

Conclusion used in the Risk Assessment – Reproductive toxicity	
Value	The NOAELs estimated for effects on fertility and development are: Parental/offspring: a NOAEL for parents and offspring could not be set since pigmentation of organs were observed in all adults at all dose levels and reduced thymus weights were observed in F1 adults and in F2 pups administered the lowest dose (i.e. 1000 ppm). Additionally, an increased incidence of hydronephrosis was observed in F1 animals administered 1000 ppm. Developmental NOAEL: 107 mg/kg bw /d
Justification for the selected value	The values are estimated from data obtained with silver zinc zeolite (considered to be worst-case) in a two-generation study in rats. This study is considered more appropriate to detect the developmental effects of silver (zinc) zeolite (see 3.10.4.1).
Classification according to CLP and DSD	Repr. 2; H361d (Suspected of damaging the unborn child), as concluded for silver zinc zeolite.

3.10.4.1 Short summary and overall relevance of the provided information on reproductive toxicity

Several studies investigating reproductive toxicity and/or developmental toxicity indicate that silver has an embryotoxic potential at doses where the mothers are not severely affected by treatment. This is mainly expressed as decreased viability in foetuses/pups and has been observed with differences in severity in developmental toxicity studies performed with silver chloride (severe effects with late post-implantation deaths, complete pup mortality, increased frequencies of hydronephrosis and cryptorchidism) and silver acetate (reduced fertility, reduced numbers of litters and implants, reduced male pup survival, reduced pup body weight and increased number of runts; reduced female and male pup weight at PN day) and in the two-generation study with silver zinc zeolite (reduced number born (15%, F1), increased stillbirth index, reduced liveborn index, reduced pup weight/pup weight gain, small/reduced weight of thymus, increased frequency of hydronephrosis). Furthermore, reduced male pup survival, reduced pup body weight and an increased number of runts were observed in a one-generation study with silver acetate.
Foetal effects are also indicated (reduced number born (11%, F1), reduced live litter size day 1(F2), reduced thymus weight) in a two generation study performed with silver sodium hydrogen zirconium phosphate (Doc IIIA, 6.8.2(03)) but similar effects were not observed in developmental toxicity studies performed with silver copper zeolite and silver sodium hydrogen zirconium phosphate (6.8.1 (02, 06).
According to the study by Shavlovski et al. (6.8.1 (03)), silver ions can displace copper ions in ceruloplasmin transporting copper to the foetus. In the study, a level of approximately 250 mg/kg bw, led to a copper deficiency that ultimately caused death of the foetuses or newborn when exposure was continuous during the entire gestation period. If exposure was restricted to the period of organogenesis (day 7-15), there were no effects observed. Shavlovski et al. explained this as likely due to a gradual decrease of active ceruloplasmin content in the blood.

Ceruloplasmin is the main copper transporter in the blood and it seems to play a role in cellular uptake of iron[17]. The concentration is usually elevated during preganancy and ceruloplasmin and copper are present in the amniotic fluid and in milk[18]. The information available is not sufficient to elucidate if the effects observed in pups are due to a deficiency of copper, iron or both. Shavlovski et al speculates that the increased mortality could be due to an impaired enzymatic protection (e.g. superoxide dismutase) against oxidative stress.
The competitive binding observed in the studies seems to be an intrinsic property of the silver ion and the severity of effect by different silver containing active substances (SCAS) thus seems to depend on the amount and release of silver and possibly other metal ions with a similar ability to compete for binding.
A reason why no effects were observed in the developmental toxicity studies with silver copper zeolite and silver sodium hydrogen zirconium phosphate could be that the amounts of silver ions released from these SCAS at the doses tested were below the LOAEL for embryo/foetal toxicity. Another reason could be that the presence of copper in silver copper zeolite is sufficient to prevent competitive binding of silver ions to ceruloplasmin. A third reason may be active ceruloplasmin still being available in the blood since the exposure period was limited to days 6-15 of gestation (as discussed by Shavlovski et al).
As discussed in the NTP study, bolus administration (gavage) is more likely to produce maternal toxicity whereas intermittent administration in feed (as in the silver chloride study) more likely produces developmental toxicity. This may explain the different results obtained in the two fertility studies with silver acetate (the 2016 study used administration via drinking water).
Based on these considerations, the lack of a second developmental toxicity study in rabbits is acceptable since the developmental effects of silver would probably not be detected in this type of study.
The estimated NOAEL for reproduction is back-calculated from the NOAEL set for silver zinc zeolite. Consequently, the estimated NOAEL for reproduction is 107 mg silver zeolite/kg bw/d.

3.10.4.2 Comparison with the CLP criteria

The results from the two-generation study with silver zinc zeolite was discussed by the Committee for Risk Assessment at ECHA (35th RAC meeting). The meeting concluded that the substance should be classified as Repr. 2; H361d (Suspected of damaging the unborn child).
There is no harmonised classification established for silver sodium hydrogen zirconium phosphate and the information available in this assessment has not been considered by RAC.

Substances with properties meeting criteria for classification are subcategorised into category 1A (known human reproductive toxicant), 1B (presumed human reproductive toxicant) or 2 (suspected human reproductive toxicant) depending on the strength of evidence.

[17] Attieh et al (1999), The Journal of Biological Chemistry.
[18] Linder, M. C et al (1998) American Journal of Clinical Nutrition, vol 67, No 5 (9655-9715) and references therein.

Classification of a substance in category 1A is largely based on evidence from humans and since no such data is available for any of the silver containing active substances, criteria for 1A are not fulfilled.
Classification of a substance in category 1B is largely based on data from animal studies. According to CLP guidance, *"such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.*"
Substances are classified in Category 2 if there is *"some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification."*

Effects on reproduction noted in the two-generation study with silver sodium hydrogen zirconium phosphate, i.e. a reduced number born in high dose F1 animals and reduced live litter size (day 1) in high dose F2 animals (and reduced thymus weight in high dose F1 and F2 pups and in male mid dose F1 pups), resemble the effects noted in the two-generation study with silver zinc zeolite. This gives support for the mode of action (silver interfering with copper transport) proposed by Shavlovski in the silver chloride study (Doc IIIA, section 6.8.1(03)) and that the treatment period used in developmental toxicity study with silver sodium hydrogen zirconium phosphate (days 6-15) was too short to detect effects as active ceruloplasmin gradually decreases in blood.
Nevertheless, even though the effects noted likely reflect the intrinsic ability of silver ions to interfere with processes crucial for foetal development, the severity of the effects caused by this substance are considered mild and not to fulfil "some evidence" of "an adverse effect on sexual function and fertility or on development in the absence of other toxic effects". This is probably a result of the lower amount of silver ion exposure from this substance compared to other silver substances.
Silver sodium hydrogen zirconium phosphate contains 10% silver and approximately 25% of the silver ions are assumed to be released during conditions assumed to mimic the GI tract. This gives an "exposure factor" for silver ion equivalents of 0.025. The corresponding exposure factor for silver zeolite is 0.014. However, although the silver ion "exposure factors" are fairly similar between these substances it is yet considered more appropriate to use data for silver zinc zeolite to fill the data gap for silver zeolite. Silver zeolite and silver zinc zeolite are chemically similar and contain a similar amount of silver that is released through ion-exchange. The actual release during real physiological conditions and thus the exact silver exposure is not known and taking also into account the lack of data for a second species, a prudent approach needs to be taken.

3.10.4.3 Conclusion on classification and labelling for reproductive toxicity

In the absence of substance-specific information, a robust classification proposal cannot be presented.
Considering the structural similarity with silver zinc zeolite and the similarity of effects observed with silver zinc zeolite and other silver salts not containing zinc, it is reasonable to assume that silver zeolite has properties fulfilling criteria for classification Repr. 2; H361d (Suspected of damaging the unborn child).

3.11 NEUROTOXICITY

Summary table of animal studies on neurotoxicity						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Duration of exposure**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
Public domain literature	According to the summary, female mice exposed to silver nitrate in drinking water for four months were less active than controls. Silver-containing deposits were found in some areas of the central nervous system with highest concentrations in areas involved in motor control (summarised in 6.9.1(03). The summary informs that early studies have reported effects on the nervous system such as weakness, rigidity of legs, loss of voluntary movement and respiratory paralysis following intraveneous administration of high doses of silver compounds to rats, dogs and guinea pigs.					IIIA 6.9 (01) Faust, R. (1992):
Public domain literature (thesis).	Exposure of foetal and adult rats to silver results in long term deposition of the metal in many structures of the nervous system. The author suggests that silver (along with other heavy metals) can be regarded as a potentially neurotoxic substance. It is not clear whether penetration of silver into parts of the peripheral nervous system causes adverse effects.					IIIA 6.9 (02) Rungby, J. (1990)

Summary table of human data on neurotoxicity				
Type of data/report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
Public domain literature	Exp I, III (i.p):1mg/mL on two successive days (total dose 1 mg), Exp II: 0.015% silver nitrate in drinking water 125 days (total dose 0.09mg)	Mice, NMRI Exp I: 20 males, 20 controls Exp III: 20 females, 20 controls Exp II: 20 females Open area test 10 days after lastexposure	Silver treated mice were hypoactive, in comparison with controls. The authors conclude that accumulations of silver may have influenced the function of the mammalian brain but recognise the methods used to test the hypothesis were crude and insufficiently specific to the CNS activity of interest.	IIIA 6.9 (03) Rungby, J., Danscher, G. (1990)
Public domain literature	Oral stick of silver nitrate (containing 0.53 g AgNO3) Woman (55 years)	Daily exposure 9 years (~124 g in total) Biopsy samples from the vestibulum oris, oral cavity and soft palate and analysed by light microscopy, electron microscopy and x-ray microanalysis.	Discoloured mucous membranes in the oral cavity Taste and smell disorders Vertigo Hypaesthesia Progressive dizziness Gait disturbances Generalised decrease in strength	IIIA 6.12(05) Westhofen, M. and Schafer, H. (1986)

Conclusion used in Risk Assessment – Neurotoxicity	
Value/conclusion	Data from repeated dose toxicity studies performed with different SCAS do not raise a specific concern for neurotoxicity.
Justification for the value/conclusion	Published information indicate a potential for accumulation of silver ions in the brains of rats. However, there are no effects observed in studies with SCAS having comparable silver contents indicating this substance to cause neurotoxic effects.

Data waiving	
Information requirement	There is no robust information available to assess the neurotoxic potential of silver zeolite or the other silver containing active substances. However, no further information is requested.
Justification	There are no effects observed among studies with SCAS (having comparable silver content) raising a concern for a neurotoxic potential of silver zeolite. The uncertainty on this endpoint is considered compensated for by the conservative approach taken when estimating NOAELs for silver zeolite based on effect levels for the silver ion equivalents (i.e. assuming that all effects are caused by silver ions).

There are no robust neurotoxicity studies available for any other silver containing active substance included in the dossier. However, in similarity with the strategy taken for other endpoints, the neurotoxic potential of silver zeolite could be estimated based on information available for each constituent of the substance, i.e. silver ions and the zeolite.

Neurotoxic potential of silver ions:
Silver sodium hydrogen zirconium phosphate: the reflexological response to stimuli (surface righting reflex, mid-air righting reflex, startle reflex, pupillary reflex) was examined in the two-generation study performed with silver sodium hydrogen zirconium phosphate. There were no treatment-related effects in the study but learning and memory tests were not included hence it is not safe to exclude that deposition of silver ions in nervous tissues could adversely affect the nervous system in fetuses/children during development.
Some information on the potential neurotoxicity of silver ions can be found in published case reports and published research.
The study summary presented in 6.12.2(05) describes a case where clinical signs such as taste and smell disorders, vertigo and hypaesthesia occurred in a patient that used a stick of silver nitrate (containing 0.53 g AgNO3) daily over a nine year period in order to treat the oral mucosa. The authors concluded that the affinity of silver for membrane and neuronal structures and the deposition of insoluble silver following extended high exposure on a daily basis had induced progression of the clinical condition of this patient.
The document submitted for 6.8.1(07) describes two other cases where neurotoxic effects have been observed in patients exposed to silver. One case presented by Sudmann (1994) describes a patient with silver-impregnated bone cement who developed serious neurological deficits five years after implantation. Two years after removal of the bone cement, the patient partially recovered from grave muscle paralysis.
The second case report (Ohbo et al, 1996) states that convulsive seizures occurred in a woman ingesting 20 mg silver (not specified) daily for 40 years. These seizures abated when silver intake was stopped.
Although these observations indicate a neurotoxic potential of silver, the limited information available in the case reports does not raise a concern high that would justify further neurotoxicity testing.
Overall, although literature data indicate an ability of silver ions to deposit in brain tissues, the data available for the different SCAS are not considered to indicate a neurotoxic potential at levels of silver ion equivalents that are comparable to silver zeolite.

Since the data on the individual constituents of silver zeolite does not raise a concern for neurotoxicity, further requests for information on acute, delayed and developmental neurotoxicity are not considered justified.

3.11.1.1 Comparison with the CLP criteria (STOT-RE)

There are no observations indicative of neurotoxicity in the studies performed with silver substances having comparable silver ion contents (i.e. silver sodium hydrogen zirconium phosphate and silver zinc zeolite).
Therefore, based on indirect testing of the individual constituents at levels comparable to those in silver zeolite, the substance is not expected to meet criteria for classification.

3.11.1.2 Conclusion on classification and labelling for neurotoxicity (STOT-RE)

There are no effects indicative of neurotoxicity observed in studies with silver zinc zeolite or silver sodium hydrogen zirconium phosphate meeting criteria for classification STOT-RE.
In the absence of substance-specific information, a robust classification proposal cannot be presented. However, based on the data available for the individual constituents of silver zeolite, there are no indications that silver zeolite has properties meeting criteria for classification.

3.12 IMMUNOTOXICITY

The dossier does not contain any studies investigating the immunotoxic potential of silver ions. Some effects noted in repeated dose toxicity studies with silver zinc zeolite and silver sodium hydrogen zirconium phosphate may reflect an immunotoxic potential (see table below) but there were no statistically significant changes on the immunological parameters included in the haematological analyses in the study with silver sodium hydrogen zirconium phosphate. Moreover, effects appear at dose levels above the guidance values for classification STOT-RE (10<C≤100) and above the critical NOAELs used for the derivation of reference values. Therefore, the findings listed in the table below are not considered to raise a concern triggering further actions.

Summary table of in vitro immunotoxicity studies						
Method, Guideline, GLP status, Reliability	**Test substance, Doses**	**Relevant information about the study**	**NOAEL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available						

Summary table of animal studies on immunotoxicity						
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Duration of exposure**	**NOEAL, LOAEL**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
OPPTS 870.3100. *GLP* *Reliability 1*	*Dog, Beagle* *4/sex*	*AlphaSan RC2000* *0, 200, 400 and 1000/700 mg/kg bw/day* *13 weeks*	***NOAEL/LOAEL (thymus)*** *400 mg/kg bw/d*	*700/1000 mg/kg bw/d* *Thymus, atrophy* *m: 2/4 (severe)* *f: 2/4 (moderate)* *Thymus, lymphoid depletion:* *m: 1/4 (severe)*	***Read across***	*IIIA* *6.4.1(05)*

OECD 416 *Oral in diet*	*Rat SpragueDawley Crl: CD® IGS BR* *28/sex*	*Silver sodium hydrogen zirconium phosphate Exp.add 9823-37 (10% Ag)* *1000, 5000 and 20000 ppm corresponding to 72.5/78.2, 363/400 and 1465/1612 mg zeomic/kg bw in F0 males and females (premating)* *approximately 1.9, 9.9 and 40 mg silver ion equivalents/kg bw/d in females)* *Maturation, mating, gestation and lactation for two successive generations*	***NOAEL/LOAEL (thymus)*** *Parental F0: 5000/20000* *Parental F1: 5000/20000* *Offspring F1:1000/5000* *Offspring F2: 1000/5000*	***Parental:*** *<u>F0 20 000ppm:</u>* *↓ thymus weight (20% m)* *↑spleen weight (m, 11%)* *<u>F0 5000ppm:</u>* *↑spleen weight (m, 20%)* *<u>F1 20 000:</u>* *↑pigmentation of thymus* *<u>F1 5000 ppm:</u>* *↑pigmentation of thymus* ***Offspring:*** *<u>F1 20 000:</u>* *thymus weight (m/f 38/32%)* *<u>F1 5000 ppm:</u>* *↓ thymus weight (m 22%)* *<u>F2 20 000:</u>* *↓ thymus weight (m/f 38/37%)* *<u>F2 5000:</u>* *↓ thymus weight (f 19%)*	*Read across*	*IIIA* *6.8.2-03* *(2002)*

[Please insert/delete rows according to the number of studies.]

Summary table of human data on immunotoxicity				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in Risk Assessment – Immunotoxicity	
Conclusion	Data indicate thymus to be a target for silver ion toxicity.
Justification for the conclusion	In studies with silver sodium hydrogen zirconium phosphate, reduced thymus weight was observed in all generations of the two-generation study in rats and thymic atrophy was observed in high dose animals in the 90 day study in dogs. Reduced thymus has been observed also in studies with silver zinc zeolite and seems thus to be a target for silver ion toxicity. However, there were no stastically significant effects on immunological parameters in the haematological analyses made in the studies with silver sodium hydrogen zirconium phosphate. Moreover, effects appear at dose levels above the guidance values for classification STOT-RE (10<C≤100) and above the critical NOAELs used for the derivation of reference values, i.e. 21 mg/kg bw/d and 6 mg/kg bw/d for medium-term and long-term exposure respectively. Therefore, the findings listed in the table below are not considered to raise a concern triggering further actions.

Data waiving	
Information requirement	There is no robust information available on the immunotoxic potential of silver zeolite.
Justification	Since there were no strong indications of an immunotoxic potential among studies performed with other silver containing active substances, this data gap is not considered to justify requests for further data. The uncertainty could be considered compensated for by the conservative approach taken for estimating NOAELs for silver zeolite (i.e. assuming all effects caused by silver ions and back-calculating NOAELs from silver zinc zeolite).

3.13 DISRUPTION OF THE ENDOCRINE SYSTEM

Summary table of in vitro studies on endocrine disruption					
Method, GuidelineGLP status, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Remarks** *(e.g. major deviations)*	**Reference**
No data available					

Summary table of animal data on endocrine disruption					
Method, Guideline, GLP status, Reliability	**Species, Strain, Sex, No/ group**	**Test substance, Dose levels, Duration of exposure**	**Results**	**Remarks** *(e.g. major deviations)*	**Reference**
No substance-specific data available.					

There is no substance-specific information available to assess the potential for endocrine disruption. Some information on the endocrine potential of the silver moiety of the substance is available from the results of studies performed with silver zinc zeolite and silver sodium zirconium hydrogenphosphate. In both these studies some weight changes of sex organs were noted in both generations. However, data indicate that organ weights could be increased in the first generation and decreased in the second thus it is not possible to conclude if these are true effects or result from normal biological variation or artefacts. The Endocrine Disruptor Expert Group (EDEG) at ECHA was consulted to advise on the data available for the two substances, the potential need for additional information and if so, the type of information needed. No firm conclusion was reached. For further information, please refer to the assessment reports for silver zinc zeolite and silver sodium zirconium hydrogen phosphate, respectively.
Based on the assumption that the ED potential of the substance is similar to silver zinc zeolite, the substance is not expected to meet the ED criteria. However, in line with recommendations in the guidance document, the applicant is requested to substantiate this by performing a literature review.

Summary table of human data on endocrine disruption				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
No data available				

Conclusion used in Risk Assessment – Endocrine disruption	
Conclusion	An assessment of the endocrine disruptor (ED) properties was conducted. However, this ED assessment could not be finalised as the data are considered insufficient for an assessment against the criteria laid down in Regulation (EU) No 2017/2100.
Justification for the conclusion	See above.

Data waiving	
Information requirement	No data required
Justification	See above

3.14 FURTHER HUMAN DATA

Summary table of further human data				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
Published re-registration document US EPA (1992)		Summary		IIIA 6.12.2(02)
Published report IRIS (US EPA) (1996)		Summary of published information.		IIIA 6.12.2(03)
Published article (1980)	Silver acetate	Case report, 47 year old woman exposed to silver acetate through anti-smoking lozenges.		IIIA 6.12.2(04)
Published article (1986)	Silver nitrate	Case report, patient using a stick of silver nitrate (containing 0.53 g AgNO3).		IIIA 6.12.2(05)
Published article (2005)	Home-made colloidal silver solution.	Case report, 58 year old man exposed to home-made colloidal silver solution.		IIIA 6.12.2(06)
Published article (2005)	Silver nitrate	Case report, fatal renal and hepatic failure in a patient following silver nitrate instillation in the renal pelvis		IIIA 6.12.2(07)
		Published report Oak Ridge Reservation Environmental Restoration Program (1992)	Summary of published information.	IIIA 6.12.2(08)

		Published article (1996) Center of Drug Evaluation and Research, Food and Drug Administration	Risk benefit assessment of silver products for medical indications	IIIA 6.12.5(01)
		Published re-registration document US EPA (1992)	Summary	IIIA 6.12.2(02)
Published re-registration document US EPA (1992)		Summary		IIIA 6.12.2(02)

Conclusion used in Risk Assessment – Further human data	
Conclusion	The human relevance of effects noted in animal studies with silver zinc zeolite and silver sodium hydrogen zirconium phosphate are supported by case reports describing argyria in humans exposed to different silver substances.
Justification for the conclusion	See text below.

Medical surveillance on manufacturing plant personnel: There is no data available for this endpoint. The applicant states "based on standard health monitoring data on workers it is not possible to correlate any adverse effect as a consequence on working with AlphaSan products".

Direct observations, e.g. clinical cases and poisoning incidents: The dossier contains no reports describing clinical cases and poisoning incidents with silver zeolite.
According to a pesticide re-registration document for silver prepared by US EPA (1992), excessive industrial and/or medicinal exposures to silver have been associated with arteriosclerosis and lesions of the lungs and kidneys. Exposure to industrial dusts containing high levels of silver nitrate and/or silver oxide may cause breathing problems, lung and throat infections and abdominal pain. Skin contact with certain silver compounds may cause mild allergic reactions such as rash, swelling and inflammation in sensitive people (6.12.2(02)).
A document on silver prepared by US EPA Integrated Risk Information System (IRIS) (6.12.2(03) refers to a publication by Gaul and Staud (1935) reporting 70 cases of generalized argyria following organic and colloidal silver medication, including 13 cases of

generalized argyria following intravenous silver arsphenamine injection therapy. The authors concluded that argyria may become clinically apparent after a total accumulated i.v. dose of approximately 8 g of silver arsphenamine.
The document states that the authors of a book entitled "Argyria, The Pharmacology of Silver" also reached the conclusion that a total accumulative i.v. dose of 8 g silver arsphenamine is the limit beyond which argyria may develop (Hill and Pillsbury, 1939). However, since body accumulates silver throughout life, it is theoretically possible that amounts less than this (for example, 4 g silver arsphenamine) can result in argyria. Therefore, based on cases presented in this study, the lowest i.v. dose resulting in argyria in one patient, 1 g metallic silver (calculated as 4 g silver arsphenamine x 0.23 (the fraction of silver in silver arsphenamine)) was considered to be a minimal effect level.
Another reference included is Blumberg and Carey (1934) who reported argyria in an emaciated chronically ill (more than 15 years) 33-year-old female (32.7 kg) who had ingested capsules containing 16 mg silver nitrate three times a day over a period of 1 year (about 30 mg silver/day) for alternate periods of 2 weeks. The authors noted that this marked argyremia was striking because even in cases of documented argyria, blood silver levels are not generally elevated to the extent observed (0.5 mg/L). Normal levels for argyremic patients were reported to range from not detected to 0.005 mg Ag/l blood. Heavy traces of silver in the skin, moderate amounts in the urine and feces, and trace amounts in the saliva were reported in samples tested 3 months after ingestion of the capsules was stopped. However, despite the marked argyremia and detection of silver in the skin, the argyria at 3 months was quite mild. No obvious dark pigmentation was seen other than gingival lines which are considered to be characteristic of the first signs of argyria. The authors suggested that this may have been the case because the woman was not exposed to strong light during the period of silver treatment. The US EPA concludes that this study is not suitable to serve as the basis for a quantitative risk assessment of silver because it is a clinical report on only one patient of compromised health. Furthermore, the actual amount of silver ingested is based on the patient's recollection and cannot be accurately determined.
The last case referred to in the IRIS document was reported by East et al. (1980) and is also presented in 6.12.2(04). The article describes argyria diagnosed in a 47-year previously healthy woman (58.6 kg) who had taken excessively large oral doses of anti-smoking lozenges containing silver acetate over a period of 2.5 years. No information was provided as to the actual amount of silver ingested. Symptoms of argyria appeared after the first 6 months of exposure. Based on whole body neutron activation analysis, the total body burden of silver in this female was estimated to be 6.4 (plus or minus 2) g. Both the total body burden and concentration of silver in the skin were estimated to be 8000 times higher than normal. In a separate 30-week experiment, the same subject retained 18% of a single dose of orally-administered silver, a retention level much higher than that reported by other investigators. East et al. (1980) cited other studies on this particular anti-smoking formulation (on the market since 1973) which demonstrated that "within the limits of experimental error, no silver is retained after oral administration." However, this may not hold true for excessive intakes like that ingested by this individual. The US EPA concludes that the study is not suitable to serve as the basis for a quantitative risk assessment.
The article presented in 6.12.2(05) describes the case where clinical signs including taste and smell disorders, vertigo and hypaesthesia occured in a patient using a stick of silver nitrate (containing 0.53 g $AgNO_3$) daily over a nine year period to treat the oral mucosa. This study is further discussed in the section on neurotoxicity.
Another case report describes blue-gray discoloration of skin in a 58 year old man who had treated himself with a colloidal silver solution that was made at home using a 38000Volt generator, 100% pure silver coins and distilled water (6.12.2(06)). The man drank 8 fluid ounces (~2.4 dl) every hour from 8 AM to 8 PM for four days without any intake of any other food or beverages. Four

weeks after self-treatment, a bluish appearance to the oral mucosa that progressed to involve the face, trunk and extremities. Examination of the patient revealed a diffuse blue-grey coloration of the skin which was most pronounced in the sun-exposed areas of forearm, hands, face, neck and the "V" of the chest. Discoloration was also noted in the lunulae, sclera, and conjunctivae of the eyes and spotty blue macules were evident on the oral mucosa of the soft palate.
Histopathological examinations of biopsies from the forearm revealed fine, minute, round, brown/black granules deposited primarily in the basement membrane around the eccrine glands and to a lesser extent in the fibrous sheath of the pilo-sebaceous units, pilo-erector muscles, dermal elastic fibres and arteriolar walls.
The increased discoloration in the sun exposed tract is explained by the combined effect of sun-induced reduction of colorless silver compounds to elemental silver and an increased melanin production due to silver stimulated melanocyte tyrosinase activity.
A case of fatal renal and hepatic failure is described in 6.12.2(07). The article describes the course of disease in a patient that underwent silver nitrate instillation in the renal pelvis for treatment of chyluria. Since the instillation was completed at a separate hospital, the authors could not confirm the dose administered to this patient.
Within 24 hours of dosing the patient developed severe renal and hepatic failure despite given N-acetyl cysteine in view of acute toxic hepatitis and placed on haemodialysis for renal failure. The case was further complicated by development of epistaxis that required post-operative ventilation support.
Although the patients' general condition and liver function tests improved by the type of dialys used, the patient died from cardiorespiratory arrest (probably caused by pulmonary embolism or aspiration pneumonia) approximately 48 hours after extubation and beginning oral feeding.
A summary of the toxicity of silver has been prepared for the Oak Ridge Reservation Environmental Restoration Program and this document has been submitted for several sections of the dossier. It is stated in the document that besides cases of localised or generalised forms of argyria, accidental or intentional ingestion of large doses of silver nitrate caused corrosive damage to the gastrointestinal tract, abdominal pain, diarrhea, vomiting, shock, convulsions and death. The estimated fatal dose of silver nitrate is ≥ 10g, but recoveries have been reported following ingestion of larger doses. Acute irritation of the respiratory tract can occur from inhalation of silver nitrate dust, but generally only at concentrations that produce argyria. One case report described severe respiratory effects in a worker who had become ill 14 hours after working with molten silver ingots.
In a study referred to (Rosenman 1979), 30 workers were exposed to silver nitrate and silver oxide dusts for periods of less than one year to greater than ten years. Twenty five individuals experienced respiratory irritation (sneezing, stuffiness, running nose or sore throat) at some time during their employment. Twenty of thirty workers reported coughing, wheezing, chest tightness and abdominal pain; the latter finding was closely correlated with blood silver levels. Granular silver-containing deposits, observed in the conjunctiva and cornea of 20/30 workers, correlated with duration of employment. Some of the workers reported decreased night vision. The eight hour time weighted average exposure (determined 4 months prior to the study) was in the range 0.039 to 0.378 mg silver/m3 for this subpopulation.
Decreased night vision was also reported in a group of workers manufacturing metal silver powder (Rosenman et al 1987). Increased excretion of the renal enzyme N-acetyl-β-D-glucosaminidase and decreased creatinine clearance seen in these workers may indicate an impaired kidney function however since the same workers were exposed to cadmium which is a known nephrotoxin, the effect cannot with certainty be ascribed to silver.

Chronic exposure to silver for reclamation workers exposed to silver and insoluble silver compounds, revealed conjunctival and corneal argyria in 21 and 25% of the workers respectively. Many also exhibited internal nasal-septal pigmentation. Examination of liver enzyme levels for silver-exposed and non-exposed workers revealed no significant differences.
Ocular damage has been reported from application of solutions containing >2% silver nitrate. Corneal opacification may be so severe as to cause blindness. Application of silver nitrate to gingival may result in necrotizing ulcerative gingivitis.
The document further states that case histories indicate that dermal exposure to silver or silver compounds for extended periods can lead to generalised skin discoloration and that mild allergic responses attributed to dermal contact with silver or silver compounds have been reported (6.12.2(08)).
A risk benefit assessment of silver products for medical indications was performed by the US Food and Drug Administration (6.12.5(01)). It is stated in the article that burn treatment with silver nitrate can cause methemoglobinemia, hydrochloridemia, hyponatremia and eschars that adhere to dressings. Silver suladiazine used to replace silver nitrate in this type of treatment may cause leucopenia and nephrotic syndrome rarely. It also states that there is a potential risk for the developing fetus when pregnant women use silver products. The results of a case-control epidemiology study suggested (after adjustment for confounding factors) some association between maternal exposures to 0.001 mg/L of silver in drinking water and some increase in fetal developmental anomalies (ear, face and neck). However, the authors of the epidemiologic study recognized that there are inferential limitations to epidemiologic studies and that further research is needed to explore these findings.
The authors of the risk-benefit assessment concluded that the lack of established effectiveness and potential toxicity of these products should be emphasized. The risk was considered to exceed the unsubstantiated benefit for over the counter silver-containing products.
Argyria is a permanent discoloration of skin and so far, antidote treatment (such as depigmentation creams, hydroquinone, dermal abrasion or chelation therapy with British antilewisite or D-penicillamnine) appears to be without effect (6.12.2(06)).

3.15 OTHER DATA

Summary table of other data				
Type of data/ report, Reliability	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
Mechanistic data: Published literature "The molecular mechanisms of copper and silver ion disinfection of bacteria and viruses"		The document provides information on the mode of action of silver ions but health effects of silver are not addressed.	Inhibition by silver occurs through interference with electron transport processes, binding to DNA and interaction with the cell membrane.	IIIA 6.10 (01) Thurman, R.B. and Charles, P.G. (1989):

Mechanistic data: Published literature "Effects of silver in isolated rat hepatocytes"			Silver nitrate or silver lactate caused dose dependent loss of cell viability in freshly isolated hepatocytes at concentrations of 30-70 µM. Silver cytotoxicity was accompanied by a decrease in hepatic thiol concentration and in increase in lipid peroxidation. Treatment of hepatocytes with the reduced glutathione (GSH)-depleting agent diethylmaleate markedly increased their vulnerability to silver toxicity whereas protective effects were produced by the thiol-reducing agent dithiothreitol. Perturbation of intracellular thiol homeostasis may play a crucial role in the mechanism underlying silver-induced lethal damage to isolated rat hepatocytes.	IIIA (6.10 -02) Baldi, C., Minoia, C., Di Nucci, A., Capodaglio, E., and Manzo, L. (1988):

Conclusion used in Risk Assessment – Other data	
Conclusion	Since there are no indications of a species-specific mechanism behind the silver toxicity observed, it must be assumed that similar effects would occur also in humans if exposed at similar dose levels
Justification for the conclusion	According to the TNsG on data requirements, studies necessary to clarify effects reported in toxicity studies (e.g. indications of non-genotoxic mechanism for carcinogenicity, species specific effects, adverse effects on reproduction, immunotoxicity or hormone related effects) should be included in section 6.10. The applicant has submitted two studies to address this data requirement but these studies do not address the major adverse effects observed in the toxicological studies with different SCAS (i.e. pigmentation of organs, increased ALP levels and histopathological changes in the liver and kidneys). The first study in the table above aims at giving a better understanding of the effects of copper and silver on bacteria and viruses at the molecular level. While this study provides some information regarding the mode of action, the relevance of this information for an understanding of the effects observed in toxicological studies is considered low. The second study is an in vitro experiment performed to determine the role of thiol modification in silver-induced toxicity to freshly isolated hepatocytes. The authors demonstrated that a time and concentration dependent cell damage occurred along with a decrease in intracellular soluble thiols and lipid peroxidation in hepatocytes isolated from male Wistar rats that had been exposed to silver nitrate and silver lactate. Since treatment with radical scavengers delayed but did not protect from cytotoxicity, silver cytotoxicity does not seem to be mediated by lipid peroxidation. The thiol reducing agent dithiothritol had protective effects whereas the glutathione depleting agent diethylmaleate potentiated silver toxicity. Based on these findings, silver was considered to cause toxic effects in rat heptocytes by disturbing the cellular thiol homeostasis. A reduced thiol pool could reduce the ability to cope with oxidative stress. This could thus be a contributing factor to the hepatic inflammation observed in the 90-day study in dogs treated with silver sodium zirconium hydrogen phosphate (6.4.1(05)). The mechanisms possibly responsible for pigmentation and effects in kidneys are only briefly discussed in the existing studies.Pigmentation of organs has been explained as an accumulation of silver in close approximation to blood vessels in different organs, in histiocytes of lymph nodes and liver, in the basement membranes of glomeruli and in the laminia propria (6.3.1(02, 03) and in Olcott (1948), evaluated in addendum 1 to section 6). It is not clear if the histopathological changes observed in the kidneys are a consequence of silver accumulation in renal structures since effects such as chronic nephritis, increased severity of corticomedullary tubular basophilia and lymphoid infiltration, interstitial fibrosis and hyaline/cellular casts have been observed also in the absence of pigmentation (silver zinc zeolite (6.4.1(06, 07)).

4 ENVIRONMENTAL EFFECTS ASSESSMENT

4.1 FATE AND DISTRIBUTION IN THE ENVIRONMENT

Silver zeolite releases silver-ions (Ag+) under the use envisaged, which is considered the active specie of the active substance. For the environmental risk assessment it is thus reasonable to focus on the fate, behaviour and effects of silver and not on the substance itself, which in most cases does not reach the environment.

Silver zeolite as a complete substance is not soluble in water.

For the environmental risk assessment it is only relevant which substances/ions of concern are released. Silver ions are released from the crystalline structure. Thus, environmental fate and effects have been addressed for silver. The other components of the active substance are not considered of environmental concern.

4.1.1 Degradation

See silver core CAR

4.1.2 Distribution

See silver core CAR

4.1.3 Bioaccumulation

See silver core CAR

4.1.4 Monitoring data

See silver core CAR

4.2 EFFECTS ON ENVIRONMENTAL ORGANISMS

The information on effects of silver on environmental organisms is provided in section 4 of the silver core CAR.

Summary table on calculated PNEC values	
Compartment	**PNEC**
Freshwater	0.008 µg/L (dissolved silver)
Sediment	44.1 µg/kg dry weight (9.58 µg/kg wet weight) (total silver)
Soil	5.6 µg/kg wet weight (total silver)
STP	0.009 mg/L (estimated total silver)

4.3 ENDOCRINE DISRUPTING PROPERTIES

Assessment of endocrine disrupting potential of silver zeolite
The endocrine disrupting properties with regard to human health are assessed and described in chapter 3.13. The mammalian data show some indications of effects on endocrine organs but the overall conclusion with regard to human health is that SZZ does not have endocrine disruption properties in humans. Based on the assumption that the ED potential of the substance is similar to silver zinc zeolite, the substance is not expected to meet the ED criteria. However, in line with recommendations in the guidance document, the applicant is requested to substantiate this by performing a literature review. If a substance is not identified as endocrine disruptor for human health, the Guidance for the identification of endocrine disruptors (ECHA/EFSA 2018) states that in this case an assessment of other non-target organisms should follow.
With regard to non-target organisms other than mammals, no information is available in the dossier that could be used for assessing endocrine disrupting properties of the active substance. The endocrine disrupting potential in the terrestrial environment is sufficiently addressed by the assessment done for human health based on mammalian data.
However, with regard to aquatic environment, it is not meaningful to assess the active substance itself, since it dissociates in water, as discussed in chapter 4.1. Therefore, we assess endocrine disrupting properties for the relevant components of the compound separately, which are silver and zeolite. This approach is also in line with the approach taken in the environmental classification of silver zinc zeolite.

Assessment of endocrine disrupting potential of silver
Early life stage toxicity studies with fish (FELS) are available for silver. None of the studies includes in vivo mechanistic (vitellogenin or spiggin induction) or EATS-mediated parameters (like gonad histopathology, sex ratio or others described in the Guidance).
In the following table, we summarise the parameters tested and results for parameters that are 'sensitive, but not diagnostic of EATS' in the available early life stage fish studies.

Fish early life stage (FELS)

a) Available FELS studies used for the environmental effects assessment (chapter 4.2 in silver core dossier)

Species	Exposure (days)	Route of exposure	Dose range (µg/L silver)	Observed parameter (positive and negative)	Effect Dose (µg/L silver)	Category of parameter	Reference and reliability
Oncorhynchus mykiss	73-77 (30d post swim-up)	water	0.06 – 1.25 (dissolved)	Survival	NOEC 1.09 µg/L (dissolved)	Sensitive to, but not diagnostic of EATS	Dethloff et al. 2007 IIIA 7.4.3.2-05 Reliability: 2
				Growth (weight)	NOEC 0.21 µg/L (dissolved)		
				Embryo time to hatch	Not affected		
				Mean day to swim-up	Not affected		
Oncorhynchus mykiss	37d	water	0.1 and 1.0 (total)	Survival	NOEC 0.1	Sensitive to, but not diagnostic of EATS	C. J. Brauner and Wood 2002a IIIA 7.4.3.2-04 Reliability: 3
				Growth	NOEC 0.1		
				Embryo time to hatch	Not affected		
				Ion regulation, ammonia and cortisol	Na+ uptake ↑ 0.1 and 1.0 Na+, K+-ATPase ↑ 0.1 and 1.0 (but decrease in larvae at 37 days post hatch) Ammonia ↑ 0.1 and 1.0 Cortisol ↑ 1.0	Indicators of alternative mode of action	
Oncorhynchus mykiss	51d post fertilisation (ca. 22d post hatch)	water	0.13 and 10.1 (dissolved)	Survival	NOEC 0.13 µg/L	Sensitive to, but not diagnostic of EATS	Colin J. Brauner and Wood 2002b) IIIA 7.4.3.2-03 Reliability: 3
				Growth	NOEC 0.13 µg/L		
				percent hatch,	inconclusive		
				percent swim-up,	inconclusive		
				degree of yolk sac absorption	Not affected		
				Ionoregulation	Results not sufficiently reliable (mortality >60%; no data for 0.1)	Indicators of alternative mode of action	
Oncorhynchus mykiss	58 d	water	0.09 and 0.9 (total)	Survival	NOEC 0.09	Sensitive to, but not diagnostic of EATS	C. J. Brauner et al. 2003) IIIA 7.4.3.2-06 Reliability: 3
				Growth (weight)	NOEC 0.09		
				Embryo time to hatch	Not affected		
				Ionoregulation	Na+ uptake inconclusive Na+, K+-ATPase ↓ 0.9 Chloride ↓ 0.9	Indicators of alternative mode of action	
Oncorhynchus mykiss	60 d	water	0.1 – 1.95 (total)	Survival	NOEC 0.36	Sensitive to, but not diagnostic of EATS	Nebeker et al. 1983 IIIA 7.4.3.2-01
				Growth (weight)	NOEC 0.1		
				Hatching success	NOEC >1.95		

Species	Exposure (days)	Route of exposure	Dose range (µg/L silver)	Observed parameter (positive and negative)	Effect Dose (µg/L silver)	Category of parameter	Reference and reliability
							Reliability: 3

b) Available FELS studies not used for the environmental effects assessment

The following studies are found in the RIVM report (Moermond, C. and van Herwijen, R. 2012; IIIA 7.4.3.2-02) but were not further assessed in the context of the environmental effects assessment. They are here presented for completeness. Reliability indicators are taken over from the RIVM report.

Species	Exposure (days)	Route of exposure	Dose range (µg/L silver)	Observed parameter (positive and negative)	Effect Dose (µg/L silver)	Category of parameter	Reference and reliability
Oncorhynchus mykiss	70	water	0.6 – 10 (total)	Survival	NOEC 0.6	Sensitive to, but not diagnostic of EATS	Davies et al. 1978 Reliability: 3
				Growth (length)	NOEC <0.6		
				Hatching (premature hatching)	NOEC 1.2		
Oncorhynchus mykiss	540	water	0.06 – 1.0 (total)	Survival	NOEC 0.09		
				Growth (length)	NOEC 0.09		
				Hatching success (premature hatching)	NOEC 0.17		
Pimephales promelas	28 post hatch	water	0.37 – 3.29 (total)	Survival	NOEC 0.37		Holcombe et al. 1983 Reliability: 2
				Growth (weight)	NOEC 0.65		
				Hatching success	NOEC 1.07		
Pimephales promelas	30	water	0.038 – 0.795 (dissolved)	Survival	NOEC 0.351		Naddy et al. 2007 Reliability: 2
				Growth (weight)	NOEC 0.351		
				Hatching success	NOEC >0.795		
Oncorhynchus mykiss	30 post hatch	water	1- 140 mg/L total, as silver thiosulfate	Survival	NOEC 35 mg/L		Leblanc et al. 1984 Reliability: 2
				Growth (length)	NOEC 16 mg/L		
				Hatching success	NOEC 64 mg/L		
Menidia beryllina	28	Seawater 10 ‰	5.5 - 100 (dissolved)	Survival	NOEC 26		Ward et al. 2006 Reliability: 1
				Growth (weight)	NOEC 26		
				Hatching success	NOEC 26		
Menidia beryllina	28	Seawater 20 ‰	24 - 440 (dissolved)	Survival	NOEC 49		
				Growth (weight)	NOEC 26		
				Hatching success	NOEC >440		
Menidia beryllina	28	Seawater 30 ‰	32 - 570 (dissolved)	Survival	NOEC 130		
				Growth (weight)	NOEC -		
				Hatching success	NOEC 130		

It is common for all available FELS studies that survival, growth and hatching were the tested parameters among those considered sensitive to, but not diagnostic of EATS. The results provide a consistent picture: Hatching is less sensitive – if sensitive at all – than survival, whereas growth is more sensitive (differences are below a factor 5). The impaired growth is likely related to the mortality.
Although the FELS test does not have endpoints that specifically respond to EDCs alone, there are limited data which show that it is responsive to certain thyroid-disrupting chemicals (OECD 150; 2018). Observed effects are arrested metamorphosis from embryo to larva, delayed hatching and malformation in zebrafish. In the present studies, if time to hatching was recorded, it was either not affected (Dethloff et al. 2007; C. J. Brauner and Wood 2002a; C. J. Brauner et al. 2003) or hatching was premature (Davies et al. 1978). In the latter study, metamorphosis was investigated (mean day to swim-up) but not found to be affected. The mammalian data do not show any adversity on thyroid weight or histopathological changes. Therefore, we conclude that there is currently no evidence for disruption of the thyroidal pathway and further *in vivo* studies with amphibians are not warranted.
Some of the FELS studies additionally investigated how silver affects ionoregulatory processes or other biochemical parameters that might provide information about the mode of action of silver toxicity in fish. The results indicate an interaction with Na+ uptake and Na+, K+-ATPase. However, the results are inconclusive. The Na+, K+-ATPase showed to be either up- or downregulated in different studies, even if conducted by the same research team under comparable conditions. We are aware of quite a body of available published research on the effect of silver on ion-regulation in fish. This literature was not considered relevant for the risk assessment of silver (i.e. for setting a PNEC), but it should be further investigated for the purpose of identification of the mode of action of silver in fish.
In the mammalian package, plausible modes of action are mention referring to the biocidal effect on target organisms and include interaction with the cell membrane, interference with electron transport processes, binding to nucleic acids, inhibition of enzymes and catalysis of free radical oxygen species.
Although the available data indicate that the toxicity of silver can be explained by a mode of action other than endocrine disruption, the available information does not allow to dismiss silver as an endocrine disruptor in non-target organisms (other than mammals) in the aquatic environment with sufficient confidence. The applicant should conduct a literature search in order to retrieve any information relevant for an assessment according to the new criteria for endocrine disruption. The literature search should include information on potential other modes of action, such as disturbance of ion regulation. The literature search should include aquatic studies with silver substances in nanoparticle-size (also called nanosilver). Depending on the outcome of this literature search, the applicant should either provide an assessment whether silver meets the new criteria for endocrine disruptors (ED) or not, or propose what kind of studies they would need to conduct. When doing this assessment, the applicant should follow the Guidance for the identification of endocrine disruptors published by ECHA.

Assessment of endocrine disrupting potential of zeolite
The crystalline, insoluble zeolite is not expected to pass biological membranes. Therefore, it is not expected to interfere with internal endocrine pathways in an organism.

References
ECHA/EFSA 2018: Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009; Drafted by EFSA and ECHA staff, with support from JRC; 07 June 2018

References for the available FELS studies not previously used for the environmental effects assessment

Davies, P. H., J. P. Goettl Jr and J. R. Sinley (1978). "Toxicity of silver to rainbow trout (Salmo gairdneri)." Water Research 12(2): 113-117.
Holcombe, G. W., G. L. Phipps and J. T. Fiandt (1983). "Toxicity of selected priority pollutants to various aquatic organisms." Ecotoxicology and Environmental Safety 7(4): 400-409.
Leblanc, G. A., J. D. Mastone, A. P. Paradice, B. F. Wilson, H. B. L. Jr and K. A. Robillard (1984). "The influence of speciation on the toxicity of silver to fathead minnow (Pimephales promelas)." Environmental Toxicology and Chemistry 3(1): 37-46.
Naddy, R. B., A. B. Rehner, G. R. McNerney, J. W. Gorsuch, J. R. Kramer, C. M. Wood, P. R. Paquin and W. A. Stubblefield (2007). "Comparison of short-term chronic and chronic silver toxicity to fathead minnows in unamended and sodium chloride-amended waters." Environ Toxicol Chem 26(9): 1922-1930.
Ward, T. J., R. L. Boeri, C. Hogstrand, J. R. Kramer, S. M. Lussier, W. A. Stubblefield, D. C. Wyskiel and J. W. Gorsuch (2006). "Influence of salinity and organic carbon on the chronic toxicity of silver to mysids (Americamysis bahia) and silversides (Menidia beryllina)." Environ Toxicol Chem 25(7): 1809-1816.

4.4 DERIVATION OF PNECS

Compartment	**PNEC**	**Remarks/Justification**
Freshwater	0.008 µg/L (dissolved silver)	Organism: Fish (*Oncorhynchus mykiss*) Endpoint: Growth of larvae. NOEC = 0.08 µg Ag/L (dissolved Ag) Assessment factor: 10 Justification: long-term tests for three trophic levels available
Sediment	44.1 µg/kg dry weight (9.58 µg/kg wet weight) (total silver)	Organism: Oligochaete (*Lumbriculus variegatus*) Endpoint: Growth. NOEC = 441 µg/kg dry weight Assessment factor: 10 Correction factor dry sediment to wet suspended matter: 4.6 Justification: see chapter 4.4 in silver core CAR
Soil	5.6 µg/kg wet weight (total silver)	Organism: Soil microbial community Endpoint: microbial carbon respiration. NOEC = 0.28 mg/kg (nominal silver in wet soil) Assessment factor: 50 No normalisation to organic matter Justification: see chapter 4.4 in silver core CAR
STP	0.009 mg/L (estimated total silver)	Organism: Activated sludge microbial community Endpoint: Respiration rate EC_{50} = 0.9 mg/L estimated based on measured concentration of

Com-part-ment	PNEC	Remarks/Justification
		test compound (see chapter 4.2.2) Assessment factor: 100 Justification: The NOEC derived from the test is not reliable. Therefore, the PNEC is calculated based on the EC_{50} with a factor of 100 (decision made by BPC Working Group V 2014).

5 ASSESSMENT OF EXCLUSION CRITERIA, SUBSTITUTION CRITERIA AND POP

5.1 EXCLUSION CRITERIA

5.1.1 Assessment of CMR properties

Criteria (BPR Article 5[1])	**Assessment**
Active substances which have been classified in accordance with Regulation (EC) No 1272/2008 as, or which meet the criteria to be classified as, carcinogen category 1A or 1B	The active substance is not classified. There is no carcinogenicity study available for silver zeolite. However, the carcinogenic potential of the individual constituents, i.e. silver ions and zeolite have been indirectly tested in a study with silver zinc zeolite which has been considered by RAC. Since no classification was proposed by RAC, **the active substance is not expected to have properties fulfilling criteria for classification as Carc. Cat. 1A or 1B.**
Active substances which have been classified in accordance with Regulation (EC) No 1272/2008 as, or which meet the criteria to be classified as, mutagen category 1A or 1B	The active substance is not classified. There are no genotoxicity studies available for silver zeolite but the individual constituents, i.e. silver ions and zeolite have been indirectly tested in studies with silver zinc zeolite. The in vitro tests in mammalian cells indicated a genotoxic potential of silver zinc zeolite which was not expressed in the in vivo comet assay. Consequently **the active substance is not expected to have properties meeting criteria for classification.**
Active substances which have been classified in accordance with Regulation (EC) No 1272/2008 as, or which meet the criteria to be classified as, toxic for reproduction category 1A or 1B	The active substance is not classified. There are no reproduction toxicity studies available for silver zeolite. However, due to the structural similarity with silver zinc zeolite and the similarity of effects observed with silver zinc zeolite and other silver salts not containing zinc, it is reasonable to assume that silver zeolite meets criteria for classification Repr. 2; H361d (Suspected of damaging the unborn child), as concluded for silver zinc zeolite. **The active substance is not expected to meet criteria to be classified as Repr. Cat. 1A or 1B.**

Conclusion on CMR properties	The exclusion criteria in BPR Article 5(1)a-c are not met.

5.1.2 Assessment of endocrine disrupting properties

Criteria (BPR Article 5)	**Assessment**
Active substances which, on the basis of the criteria specified pursuant to the first subparagraph of paragraph 3 are considered as having endocrine-disrupting properties that may cause adverse effects in humans and to the environment.	The data available is considered insufficient to assess the endocrine properties of silver zeolite. Consequently, no conclusion can be drawn whether silver zeolite fulfils criterion (d) of Article 5(1) for human health or criterion (e) of Article 10(1) for the environment.

Criteria (BPR Article 5)	**Assessment**
Pending the adoption of those criteria[1], active substances that are classified in accordance with Regulation (EC) No 1272/2008 as, or meet the criteria to be classified as, carcinogen category 2 and toxic for reproduction category 2[2].	The active substance has no harmonised classification for carcinogenicity and is not expected to fulfil criteria for Carc. Cat. 2 (see 5.1.1). The active substance has no harmonised classification for reproductive toxicity but is expected to fulfil criteria criteria for Repr. Cat. 2 (see 5.1.1).
Substances such as those that are classified in accordance with Regulation (EC) No 1272/2008 as, or that meet the criteria to be classified as, toxic for reproduction category 2 and that have toxic effects on the endocrine organs[3].	The active substance has no harmonised classification for reproductive toxicity but is expected to fulfil criteria criteria for Repr. Cat. 2 (see 5.1.1). The active substance is not expected to have toxic effects on endocrine organs.
Active substances which are identified in accordance with Articles 57(f) and 59(1) of Regulation (EC) No 1907/2006 as having endocrine disrupting properties	The active substance has not been identified as having endocrine disrupting properties.

[1] This refers to the criteria mentioned in the first row.
[2] These active substances shall be considered as having endocrine-disrupting properties
[3] These active substances may be considered as having endocrine-disrupting properties

Conclusion on ED properties	The data available is considered insufficient to assess the endocrine properties of silver zeolite. Consequently, no conclusion can be drawn whether silver zeolite fulfils criterion (d) of Article 5(1) for human health or criterion (e) of Article 10(1) for the environment.

5.1.3 PBT Assessment (following Annex XIII to Regulation (EC) No 1907/2006)

PBT assessment is not applicable to inorganic substances according to ECHA 2008 (Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment). This REACH guidance is directly applicable to biocides according to the document "The relevance of REACH Guidance Documents for dossier evaluation under the Biocidal Products Directive 98/8/EC" (endorsed at the 35th meeting of Member States Competent Authorities for the implementation of Directive 98/8/ EC).

Summary and overall conclusions on PBT or vPvB properties

Overall conclusion:

Based on the argument provided above, the substance is not a PBT / vPvB substance.

5.2 SUBSTITUTION CRITERIA

Substitution criteria (BPR, Article 10)	**Assessment**
One of the exclusion criteria listed in Article 5(1) is met but AS may be approved in accordance with Article 5(2)	Criteria not fulfilled
The criteria to be classified, in accordance with Regulation (EC) No 1272/2008, as a respiratory sensitiser is met	Criteria not fulfilled
The acceptable daily intake, acute reference dose or acceptable operator exposure level, as appropriate, is significantly lower than those of the majority of approved active substances for the same product-type and use scenario	Criteria not fulfilled
Two of the criteria for being PBT in accordance with Annex XIII to Regulation (EC) No 1907/2006 are met	Not applicable
There are reasons for concern linked to the nature of the critical effects which, in combination with the use patterns, amount to use that could still cause concern, such as high potential of risk to groundwater, even with very restrictive risk management measures	No concern
The AS contains a significant proportion of non-active isomers or impurities.	Not met

Conclusion on substitution criteria	The substitution criteria in BPR Article 10(1)a-f are not met.

5.3 ASSESSMENT OF LONG-RANGE ENVIRONMENTAL TRANSPORTATION AND IMPACT ON ENVIRONMENTAL COMPARTMENTS

Conclusion on LRTAP/POP asessment	POP criteria not applicable to a purely inorganic substance. There are no indications (monitoring data or modelling data) of any long range transport potential of the active substance.

Part B Exposure assessment and effects of the active substance in the biocidal product(s)

6 GENERAL PRODUCT INFORMATION

6.1 IDENTIFICATION OF THE PRODUCT

Name(s) of the product	
Trade name(s) or proposed Trade name(s)	Agion Antimicrobial Type LGK
Manufacturer's development code and number of the product	Zeomic Type LGK Silver Zeolite A Product Code LGK10T
Fromulation type	Powder for use in treated articles

6.2 COMPLETE QUALITATIVE AND QUANTITATIVE COMPOSITION OF THE BIOCIDAL PRODUCT

Active substance(s)					
ISO or Trivial name	**IUPAC name or other accepted chemical name**	**EC number**	**CAS number**	**Composition / all constituents (upper and lower concentration limit in % (w/w))****	**Concentration in the product in % (w/w)**
Silver zeolite	Silver zeolite (Zeolite, LTA framework type, ion-exchanged with silver ions) This entry covers LTA framework type zeolite which has been ion-exchanged with silver ions at a content of Ag 0.5%-6% (dry weight basis) and with NH_4 at a level <3% in the presence of moisture	-	130328-18-6	5% w/w silver The exact composition in %w/w for the other constitiuents is given in the Confidential Annex	100*

* The representative biocidal product consists of 100% of the technical active substance with a minimum purity of 99%

** The content of elements of concern are disclosed. The full composition is provided in the Confidential Annex. The concentration given are those taken from Document III section B2.2 (i.e. based on the information provided by the applicant). Analytical data is also available showing slightly different concentrations (see further the Confidential Annex).

Other components / ingredients of the product

ISO or Trivial name	IUPAC name or other accepted chemical name	EC num-ber	CAS number	Concentration in in the product in % (w/w)	Func-tion
Not relevant – The representative biocidal product consists of 100% of the active substance					

6.3 PHYSICAL, CHEMICAL AND TECHNICAL PROPERTIES

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Physical state at 20°C and 101.3 kPa	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: powder at 25°C	OPPTS 830-6303 (visual assessment)	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid).	Shepler (2001) IIIA 3.3.1-01
Colour at 20°C and 101.3 kPa	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: white at 25°C	OPPTS 830-6302 (visual assessment)	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid).	Shepler (2001) IIIA 3.3.2-01
Odour at 20°C and 101.3 kPa	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: odourless at 25°C	OPPTS 830-6304 (olfactory assessment)	The result is considered valid also for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid).	Shepler (2001) IIIA 3.3.3-01
Acidity / alkalinity	Silver copper zeolite (Agion Silver Antimicrobial Type AC), 3.5% silver: pH of a 1% suspension in water was 9.1.	CIPAC Method 75	The result may not be fully representative for silver zeolite. However, it is not assumed that the pH of silver zeolite would be >10 given that the alkaline constituents are in the same concentration range as in the tested material.	Cunningham (2001) III A3.1.1-01
Relative density	<u>Bulk (pour) density</u> Zeomic Type LGK Silver Zeolite A : 0.5 g/cm^3	Not stated	The lack of relative density data is not considered a concern since this parameter is not crucial for the risk assessment. It was concluded in the peer-review that data from for example SDS would acceptable. The information provided is thus considered acceptable.	EPA Statement of Formula

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
	Silver zinc zeolite (Agion Silver Antimicrobial Type AJ), 2.5% silver: 0.5 g/cm^3	OPPTS 830.7300 (equivalent to CIPAC MT 33)		Shepler (2001) IIIA 3.3.3-01
Storage stability, stability and shelf-life				
Accelerated storage	No data			
Long term storage at ambient temperature	There were no significant changes in any of the measured parameters for both storage conditions (see further below). The water content is claimed in the conclusion to increase during storage but this cannot be interpreted from the raw data. <u>Warehouse conditions</u> Ag: N-grade 0 months: 2.79 ± 0.02 (N=5) 12 months: 2.80 ± 0.02 (N=5) D-grade 0 months: 3.50 ± 0.02 (N=5) 12 months: 3.50 ± 0.02 (N=5) H-grade 0 months: 3.68 ± 0.03 (N=5) 12 months: 3.68 ± 0.03 (N=5) Cu:	Silver copper zeolite (Zeomic AC10D, 3.5% silver; N, D and H grade; see further the confidential Annex to silver copper zeolite CAR) was stored for 12 months in commercial packaging (polyethylene bags in air-dry pail cans) stored under warehouse conditions (max: 42.1 °C, min: 2.3 °C, mean: 18.9°C; RH not measured) and elevated temperature (40-45°C, mean 42°C) Parameters determined: Silver, copper and sodium by X-ray fluorescence. Ammonium by inonaphtol colourimetric method. Alumino silicate by calculation. Water by loss on ignition. pH as a 1% suspension in water. Particle size by laser scanning.	The studies were not according to GLP but considered acceptable. In principle the data is considered representative for silver zeolite given the similarities of the materials (i.e. inorganic crystalline solid) and the fact that the product cannot degrade (conclusion agreed at APCP WG V 2017). However, the product can abstract water which may result in a change of particle size which in the end may affect the efficacy and the performance of the product. No such significant change was shown for the tested formulations but further bridging data (e.g. particle size data of aged product) may be requested for product authorisation at MS-level. The shelf-life needs also to be claimed and supported by relevant data (i.e. further	Uchida, 2001 (B3.7-01 Confidential)

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	Refer-ences
	N-grade 0 months: 4.80 ± 0.05 (N=5) 12 months: 4.80 ± 0.05 (N=5) D-grade 0 months: 6.02 ± 0.03 (N=5) 12 months: 6.02 ± 0.03 (N=5) H-grade 0 months: 6.24± 0.05 (N=5) 12 months: 6.24 ± 0.05 (N=5) Elevated temperature Ag: N-grade 0 months: 2.79 ± 0.02 (N=5) 12 months: 2.79 ± 0.02 (N=5) D-grade 0 months: 3.50 ± 0.02 (N=5) 12 months: 3.50 ± 0.02 (N=5) H-grade 0 months: 3.68 ± 0.03 (N=5) 12 months: 3.68 ± 0.03 (N=5) Cu: N-grade 0 months: 4.80 ± 0.05 (N=5) 12 months: 4.80 ± 0.05 (N=5) D-grade 0 months: 6.02 ± 0.03 (N=5) 12 months: 6.02 ± 0.03 (N=5) H-grade 0 months: 6.24± 0.05 (N=5)	X-ray diffraction pattern Scanning electronic microscopy Microbiological analysis for *Staphylococcus aureus* IFO12732 and *Escherichia coli* IFO3972	data may be needed if shelf-life >12 months is claimed).	

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
	12 months: 6.24 ± 0.05 (N=5) pH, warehouse conditions N-grade 0 months: 9.68 ± 0.08 (N=5) 12 months: 9.67 ± 0.08 (N=5) D-grade 0 months: 9.20 ± 0.05 (N=5) 12 months: 9.19 ± 0.04 (N=5) H-grade 0 months: 9.24± 0.05 (N=5) 12 months: 9.23 ± 0.05 (N=5) pH, elevated temperature N-grade 0 months: 9.68 ± 0.08 (N=5) 12 months: 9.70 ± 0.08 (N=5) D-grade 0 months: 9.20 ± 0.05 (N=5) 12 months: 9.20 ± 0.07 (N=5) H-grade 0 months: 9.24± 0.05 (N=5) 12 months: 9.25 ± 0.08 (N=5) The specific results for other parameters are considered confidential (see further the confidential Annex to the CAR on silver copper zeolite)			
	There were no significant changes in any of the measured parameters for both storage	Silver zinc zeolite (Zeomic AJ10D, 2.5% Ag) was stored under the same conditions		Uchida, 2000

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
	conditions (see further below). The water content is claimed in the conclusion to increase during storage but this cannot be interpreted from the raw data. <u>Warehouse conditions</u> Ag: N-grade 0 months: 2.15 ± 0.01 (N=5) 12 months: 2.15 ± 0.02 (N=5) D-grade 0 months: 2.45 ± 0.02 (N=5) 12 months: 2.45 ± 0.02 (N=5) H-grade 0 months: 2.68 ± 0.03 (N=5) 12 months: 2.68 ± 0.03 (N=5) Zn: N-grade 0 months: 12.37 ± 0.2 (N=5) 12 months: 12.36 ± 0.2 (N=5) D-grade 0 months: 14.28 ± 0.3 (N=5) 12 months: 14.29 ± 0.3 (N=5) H-grade 0 months: 14.79 ± 0.2 (N=5) 12 months: 14.79 ± 0.2 (N=5) Elevated temperature Ag: N-grade	and using the same procedures as in the study above.		(B3.7-02 Confidential)

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	Refer-ences
	0 months: 2.15 ± 0.01 (N=5) 12 months: 2.15 ± 0.01 (N=5) D-grade 0 months: 2.45 ± 0.02 (N=5) 12 months: 2.49 ± 0.08 (N=5) H-grade 0 months: 2.68 ± 0.03 (N=5) 12 months: 2.68 ± 0.02 (N=5) Zn: N-grade 0 months: 12.37 ± 0.2 (N=5) 12 months: 12.36 ± 0.2 (N=5) D-grade 0 months: 14.28 ± 0.3 (N=5) 12 months: 14.28 ± 0.3 (N=5) H-grade 0 months: 14.79± 0.2 (N=5) 12 months: 14.79 ± 0.2 (N=5) pH, warehouse conditions N-grade 0 months: 9.08 ± 0.09 (N=5) 12 months: 9.10 ± 0.08 (N=5) D-grade 0 months: 9.15 ± 0.07 (N=5) 12 months: 9.20 ± 0.05 (N=5) H-grade 0 months: 9.20± 0.06 (N=5) 12 months: 9.19 ± 0.03 (N=5) pH, elevated temperature			

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
	N-grade 0 months: 9.08 ± 0.09 (N=5) 12 months: 9.10 ± 0.10 (N=5) D-grade 0 months: 9.15 ± 0.07 (N=5) 12 months: 9.15 ± 0.05 (N=5) H-grade 0 months: 9.20 ± 0.06 (N=5) 12 months: 9.20 ± 0.05 (N=5) The specific results for other parameters are considered confidential (see further the confidential Annex to the CAR on silver zinc zeolite)			
Low temperature stability (liquids)	Low temperature stability (liquids)	Not relevant- the product is not in liquid form		
Effects on content of the active substance				
Light	No data			
Temperature and humidity	Covered by storage stability above			
Reactivity towards container material	Covered by storage stability above			
Technical characteristics				

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
The formulation is to be incorporated into polymers and none of the technical characteristics are considered relevant for that use pattern (with the exception for particle size distribution which is presented below).				
Particle size distribution, content of dust / fines, attrition, friability	Agion Silver Antimicrobial Type LGK, 4-6% silver: Particle size in the particle volume distribution Mean particle size 8.4 to 9.1 µm. Min: ~0.5 µm	Laser scanning particle size measurement	Results provided in inspection certifcates. However, the results are suffcienlty reported and thus accepted.	Inspection Certificates Type LGK Doc IV **Confidential** (IIIB 3.11-01)
Physical and chemical compatibility with other products including other biocidal products with which its ues is to be authorised				
Physical compatibility	No data		Agion Silver Antimicrobial Type LGK is not intended to be used with other biocidal active ingredients.	
Chemical compatibility	No data		Agion Silver Antimicrobial Type LGK is not intended to be used with other biocidal active ingredients.	
Degree of dissolution and dilution stability	Not data		Agion Silver Antimicrobial Type LGK is not a tablet or soluble bag formulation nor is it soluble in water.	
Surface tension	No data		Agion Silver Antimicrobial Type LGK is not a liquid formulation	
Viscosity	No data		Agion Silver Antimicrobial Type LGK is not a liquid formulation	

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Physical hazards and characteristics				
Explosives	It is considered that the material is not explosive as the material does not contain any functional groups known to confer explosive properties		Valid justification	
Flammable gases	Not relevant			
Flammable aerosols	Not relevant			
Oxidising gases	Not relevant			
Gases under pressure	Not relevant			
Flammable liquids	Not relevant			
Flammable solids	Not considered highly flammable as it has no capacity to initiate or support combustion, all components are inorganic and non-pyrophoric.		Valid waiver under CLP (inorganic substance known to be stable)	
Self-reactive substances and mixtures	Data lacking		Given the nature of active substance / biocidal product (purely inorganic crystalline solid containing no reactive elements) it is not anticipated to be self-reactive.	
Pyrophoric liquids	Not relevant			

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Pyrophoric solids	Data lacking		Based on experience in use and the nature of the active substance / biocidal product it is concluded that it is not a pyrophoric solid.	
Substances and mixtures which in contact with water emit flammable gases	Data lacking		Based on experience in use and the nature of the active substance / biocidal product (purely inorganic crystalline solid containing no reactive elements) it is concluded that it does not emit flammable gases in contact with water.	
Oxidising liquids	Not relevant			
Oxidising solids	Data lacking		Based on structure the compound is neither an oxidizer nor a reducer. However, since the inorganic substance contains oxygen the waiver according to CLP does not apply.	
Organic peroxides	Not relevant			
Corrosive metals	Data lacking		Although the dossier was submitted under BPR, the document III's were prepared in accordance with the templates under BPD. This data point was thus not addressed. As for the active substance, the biocidal product is not anticipated to be corrosive against metal	
Auto-ignition temperature	Not relevant			

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
of products (liquid and gas)				
Relative self-igniton temperature of solids	Data lacking		Based on experience in use and the nature of the active substance / biocidal product (purely inorganic crystalline solid containing no reactive elements) it is not anticipated to have a relative self-ignition temperature <400°C. Parameter not relevant for classification purposes	
Dust explosion hazard	Data lacking		Although the dossier was submitted under BPR, the document III's were prepared in accordance with the templates under BPD. This data point was thus not addressed. However, since Agion Silver Antimicrobial Type LGK appears to fulfil the waiving critreria (i.e. inorganic substance that cannot be oxidised), it should be exempt from testing.	

6.4 HAZARD IDENTIFICATION FOR PHYSICAL AND CHEMICAL PROPERTIES

The representative biocidal product consists of 100% of silver zeolite complying with the generic definition given in part A, section 1.1. In line with the hazard identification for the active substance (see part A, section 1.5) it can thus be concluded that there are no hazards identified in relation to the physical and chemical properties of the biocidal product.

6.5 ANALYTICAL METHODS FOR DETECTION AND IDENTIFICATION

Introduction
As explained in part A, section 1.6 only analytical methods for the active substance and relevant components in the representative biocidal product are discussed here.

Evaluation
1. Analysis of the active substance in the biocidal product
The biocidal product consists of 100% of the active substance. Hereby, the analytical method for the biocidal product is the same as presented in Part A, section 1.6 for the active substance as manufactured. For transparency the method is listed in the table below as well.

2. Monitoring methods for relevant components of the biocidal product
Silver is the only component of the biocidal product considered relevant for monitoring in the different compartments. Methods for this analyte is addressed in part A, section 1.6.

Analytical methods for the analysis of the active substance as manufactured including impurities and impurities									
Analyte (type of analyte e.g. active substance or impurities)	**Analytical method**	**Fortification range / Number of measurements**	**Linearity**	**Specificity**	**Recovery rate (%)**			**Limit of quantification (LOQ) or other limits**	**Reference**
					Range	Mean	RSD		
Silver, copper and other main components and potential (heavy metal) impurities.	Full dissolution/digestion in a mixture of HF/HNO_3 (1:4) followed by analysis with ICP-OES	4% (main elements) 100 ppm (remaining elemnts)	The tested linearity range for main components was 0.02-2.0 ppm. Remaining elements were tested in the range of 0.004-1.0 or 0.02-0.5 ppm. Correlation coefficient 1.0 for all elements tested.	ICP-OES is a specific method as all elements are determined at a unique wavelength.	Mean range: 89-126	Not relevant	0.2-5.6%	LOD: 4 ppm (As, Cd, Cr) 20 ppm (remaining elements)	Drinkard, P. (2016) Confidential Annex

7 EFFICACY

7.1 EFFICACY

Agion Antimicrobial Type LGK is used in the manufacture of a range of treated articles. The applicant did not describe their claims in a clear manner in the original dossier, but somewhat diffuse antimicrobial claims were made. Efficacy was impossible to assess on the basis of these claims. In addition, the submitted efficacy studies were not allocated to specific PTs. On request, more precise claims, use areas and example uses for every PT were provided by the applicant (see document: "Efficacy information silver zeolite"). Where PT allocations of the submitted tests were lacking, the eCA has assumed a PT on the basis of which organisms were tested and which test conditions were applied. Likewise, where claims were not formulated sufficiently clearly in order to demonstrate them, they have been reformulated more precisely by the eCA, trying to assume what the intention of the claims given by the applicant was. Please see also chapter 2 for further explanations. In the absence of clear rules how to deal with a wide variety of applications, the applicant was asked to give example uses per PT. The assessment of the efficacy studies is made against the assumed use conditions of these example uses.
At a late stage (Spring 2017), additional efficacy tests were submitted (5.10.2.03-05), this time explicitly allocated to *all* PTs and with a reference to the respective example uses.

Experimental data on the efficacy of the biocidal product against target organism(s)								
Function	**Material tested**	**Test substance**	**Test organism(s)**	**Test method**	**Test system / concentrations applied / exposure time**	**Test results: effects**	**Reference**	**Remarks**
Treatment of or incorporation into materials, surfaces or articles to reduce cross-contamination								No tests provided which show killing on contact
Treatment of or incorporation into materials, surfaces or articles with the purpose of preventing microbial growth	*Polyurethane, 12,5% loading, Carbon, 2% loading*	*AgIon Silver zeolite Type LGK*	*S. aureaus, E.coli, C. albicans*	1. Shake flask method (ASTM E2149). 2. Direct inoculum method according to ASTM E2180-01, JIS 22801, ISO 22196	1: 24 h 2: 30 min – 2 hours	99,999% growth reduction	*Partenaude, L. (2015) III B 5.10.2-01*	Test not acceptable due to too high loading rates, material not representative for the example use and not enough species of bacteria tested.
"	*PE fabric, Powder coated Al and metal, PVC film, ABS Know, HDPE, Polycaprolatone PP Coupons, HIPS Door liner, PC, PP, TPR, LDPE, Coated ceramic tiles, Pellethane, Fabric*	*Agion Antimicrobial Type(s) AC (0,3-5%), AJ (0,5-5%) and AK (0,5-5%)*	*S. aureus, MRSA, E. coli, P. aeruginosa, S. choraesuis, L. monocytogenes, C. albicans, S. epidermidis, K. pneumoniae* *A. niger Stachybotrys chatarum*	1. Shake flask method (ASTM E2149). 2. Direct inoculum method according to ASTM E2180-01, JIS 22801, ISO 22196 3: Fungus Test method (ASTM-G21)	1: 24 h 2: 30 min – 2 hours 3: 28 days	Log 2 – log 5 reduction for bacteria and C. albicans 0-2 (no growth to slight growth for A.niger)	*Foster, L. (2011) IIIB 5.10.2-02*[16]	Test not acceptable;carried out with silver zinc zeolite (typ AJ and AK) and silver copper zeolite (typ AC)

"	*LDPE (Low density polyethylene)*	*Agion Antimicrobial Type LGK (5%)*	*E. coli, S. aureus, P. aeruginosa, Listeria monocytogenes*	ISO 22196:2011(E)	Film covered samples, 5% LGK content, 24h (37°C)	See table further down	*Duan, T. (2017) IIIB 5.10.2*-03[19]	
"	*LDPE (Low density polyethylene)*	*Agion Antimicrobial Type LGK (5%)*	*E. coli, S. aureus, P. aeruginosa, Listeria monocytogenes*	*LDPE samples were inoculated 5 times and the resulting CFU were counted after 5 days.*	*Not covered, 5% AC content, 5 days, periodic humidity scheme, 6h 85-90%, 18 h 50-60%, 5 consecutive inoculations*	See table further down	*Duan, T. (2017) IIIB 5.10.2-04*[16]	
"	*LDPE (Low density polyethylene)*	*Agion Antimicrobial Type LGK (5%)*	*A. niger P. varioti T. virens*	*LDPE samples were inoculated 5 times and the resulting CFU were counted after 5 days.*	*Not covered, 5% AC content, 5 days, periodic humidity scheme, 6h 85-90%, 18 h 50-60%, 5 consecutive inoculations*	See table further down	*Duan, T. (2017) 5.10.2.05*[16]	No growth in controls

[19] Test carried out with AgION Antimicrobial type(s) AC, AK, LGK. Only the results for the tests with the copper form (AC) are presented here

Test results 5.10.2-03

Sample	Test organism	Inoculation (t = 0) (CFU)	24 hour contact (CFU)	Percent Reduction	Antibacterial activity (R Value)
LDPE Control	P. aeruginosa	2.2×10^4	2.8×10^7 (log 7.5)	--	
LDPE + 5% Type LGK	P. aeruginosa	--	<10	99.9999%	6.5
LDPE Control	S. aureus	2.2×10^4	2.9×10^5 (log 6.5)	--	
LDPE + 5% Type LGK	S. aureus	--	<10	99.999%	5.5
LDPE Control	E. coli	2.0×10^4	2.9×10^7 (log 7.5)	--	
LDPE + 5% Type LGK	E. coli	--	<10	99.9999%	6.5
LDPE Control	Listeria monocytogenes	2.1×10^4	3.8×10^5 (log 5.6)	--	
LDPE + 5% Type LGK	Listeria monocytogenes	--	<10	99.99%	4.6

Test results 5.10.2-04a: S. aureus

Sample	Added inoculation at day 1, 2, 3, 4, 5*	Leached samples (CFU) post incubation	Percent Reduction	Non-leached samples (CFU) Post incubation	Percent Reduction
LDPE Control	Sum: 1.6×10^6 Mean: 3.2×10^5	4.1×10^5	No growth	3.6×10^5	No growth
LDPE + 5% Type LGK		<10	99.99%	<10	99.99%

Inoculum =2.8×10^5, 3.2×10^5, 2.9×10^5, 3.3×10^5, 3.6×10^5 CFU/ml –day 1, 2, 3, 4, 5, respectively (no growth in controls).
<10 CFU = Limit of detection of the assay.
Results are the mean of triplicate determinations.

Test results 5.10.2-04-b: E coli

Sample	Added inocu-la-tion at day 1, 2, 3, 4, 5*	Leached samples (CFU) post incubation	Percent Re-duction	Non-leached samples (CFU) post incubation	Percent Re-duction
LDPE Control	Sum: 2.1 x 10^7 Mean: 4.2 x 10^5	5.7 x 10^6	--	3.7 x 10^6	--
LDPE + 5% Type LGK		<10	99.999%	<10	99.999%

Inoculum = 4.2 x 10^5, 3.9 x 10^5, 5.0 x 10^5, 3.3 x 10^5, 4.6 x 10^5, CFU/ml –day 1, 2, 3, 4, 5, respectively.
<10 CFU = Limit of detection of the assay.
Results are the mean of triplicate determinations.

Test results 5.10.2-04-c: P. aeruginosa

Sample	Added inocu-la-tion at day 1, 2, 3, 4, 5*	Leached samples (CFU) post incubation	Percent Re-duction	Non-leached samples (CFU) post incubation	Percent Re-duction
LDPE Control	Sum: 2.0 x 10^7 Mean: 4.1 x 10^5	3.8 x 10^6	--	3.6 x 10^6	--
LDPE + 5% Type LGK		<10	99.999%	<10	99.999%

Inoculum = 4.2 x 10^5, 3.4 x 10^5, 3.3 x 10^5, 4.8 x 10^5, 4.6 x 10^5 CFU/ml – day 1, 2, 3, 4, 5, respectively.
<10 CFU = Limit of detection of the assay.
Results are the mean of triplicate determinations.

Test results 5.10.2-04-d: Listeria monocytogenes

Sample	Added inocu-la-tion at day 1, 2, 3, 4, 5*	Leached samples (CFU) post incubation	Percent Re-duction	Non-leached samples (CFU) post incubation	Percent Re-duction
LDPE Control	Sum: 1.4 x 10^6 Mean: 2,4 x 10^5	4.6 x 10^5	--	3.2 x 10^5	--
LDPE + 5% Type LGK		<10	99.99%	<10	99.99%

Inoculum = 2.8 x 10^5, 3.0 x 10^5, 2.2 x 10^5, 3.3 x 10^5, 2.9 x 10^5 CFU/ml –day 1, 2, 3, 4, 5, respectively (no growth in controls).
<10 CFU = Limit of detection of the assay.
Results are the mean of triplicate determinations.

Test results 5.10.2-05a: A. niger

Sample	Added inoculation at day 1, 2, 3, 4, 5*	Leached samples (CFU) post incubation	Percent Reduction	Non-leached samples (CFU) post incubation	Percent Reduction
LDPE Control	Sum: 1.0 x 10^6 Mean: 2.1 x 10^5	2.0 x 10^5	No growth	1.6 x 10^5	No growth
LDPE + 5% Type LGK		<10	99.99%	<10	99.99%

Inoculum = 2.2 x 10^5, 1.9 x 10^5, 2.0 x 10^5, 1.8 x 10^5 2.5 x 10^5 CFU/ml day 1, 2, 3, 4, 5 respectively (no growth in controls).
<10 CFU = Limit of detection of the assay.
Results are the mean of triplicate determinations using the standard plate method. The results using the TEMPO method showed slightly less reduction (99.95 and 99.93% for leached/unleached samples respectively).

Test results 5.10.2-05b: P varioti

Sample	Added inoculation at day 1, 2, 3, 4, 5*	Leached samples (CFU) post incubation	Percent Reduction	Non-leached samples (CFU) post incubation	Percent Reduction
LDPE Control	Sum: 1.4 x 10^5 Mean: 2.8 x 10^4	3.1 x 10^4	No growth	2.7 x 10^4	No growth
LDPE + 5% Type LGK		<10	99.97%	<10	99.96%

Inoculum = 2.3 x 10^4, 3.0 x 10^4, 2.9 x 10^4, 2.8 x 10^4, 3.0 x 10^4 CFU/ml – day 1, 2, 3, 4, 5 respectively (no growth in controls).
<10 CFU = Limit of detection of the assay.
Results are the mean of triplicate determinations using the standard plate method. The results using the TEMPO method showed slightly less reduction (99.52 and 98% for leached/unleached samples respectively).

Test results 5.10.2-05c: T virens

Sample	Added inoculation at day 1, 2, 3, 4, 5*	Leached samples (CFU) post incubation	Percent Reduction	Non-leached samples (CFU) post incubation	Percent Reduction
LDPE Control	Sum: 1.9 x 10^5 Mean: 3.8 x 10^4	3.7 x 10^4	No growth	3.3 x 10^4	No growth
LDPE + 5% Type LGK		<10	99.97%	<10	99.97%

Inoculum = 4.4 x 10^4, 3.9 x 10^4, 3.2 x 10^4, 4.0 x 10^4, 3.5 x 10^4 CFU/ml – day 1, 2, 3, 4, 5 respectively (no growth in controls).
<10 CFU = Limit of detection of the assay.
Results are the mean of triplicate determinations using the standard plate method. The results using the TEMPO method showed slightly less reduction (99 and 99% for leached/unleached samples respectively).

PT 2

None of the studies originally provided was allocated to PT 2. The studies *5.10.2-01, 5.10.2-02*, were selected by the eCA to possibly represent PT 2 applications. The studies 5.10.2-03, -04 and -05 submitted in February and March 2017 were allocated to PT 2, 4 and 7 . Two example uses were given for PT 2: i) wall or floor covering, ii) air conditioning components. The use conditions given by the applicant are "indoors" and intended areas of use are such which are "humid" and "conducive to bacterial growth". A bacteriostatic claim has been made.

For example use 1, wall or floor covering, the problem description by the applicant was "untreated surface of the article presents a risk for cross contamination of bacteria". This was translated to a fast bacteriocidal effect (5-60 min) according to the requirements for liquid disinfectants. To prevent cross-contamination, rather short contact times and simulation of a splash contamination in combination with otherwise dry test-conditions are required. The submitted tests do not represent that. In conclusion, efficacy for example-application 1 is not demonstrated.

For example use 2 (air conditioning components), the test submitted under *IIIB 5.10.2-01* is not appropriate to show efficacy; further test-organisms are lacking (efficacy for PT 2 should be shown against 2 gram-positive and 2 gram-negative bacteria). The tested materials are not representative for uses in PT 2 (polyurethane is typically used for foams for which anti-odour claims under PT 9 are more likely, carbon is rather a material for PT 4 applications). Finally, the material was loaded with higher amounts of silver zeolite (12,5%) than described under "overall use pattern" (5%).
The applicant requested to accept efficacy for PT 2 on the basis of read-across to data for silver zinc zeolite (IIIB 5.10.2-02). The reasoning is based on the demonstration of equivalent silver release for silver zeolite and silver zinc zeolite and the applicant refers to release studies located under IIIA 3.5-02 and IIIA 3.5-03. According to the applicant, the existing data for silver zinc zeolite represents a relevant assessment as similar (or higher) silver content may be used with silver zeolite and the release profile of silver zinc zeolite and zeolite is comparable.

The eCA does not accept this reasoning. Read across was accepted for silver zinc zeolite from a test based on silver zeolite. From an efficacy point of view, silver zeolite without any additional ions of other metals is the worst case; silver zeolite and silver zinc/copper zeolite seem to release the same amount of silver ions. However, additional copper and zinc ions are released by the two named substances, which both are known to have biocidal effects. Therefore, read-across from silver zeolite to silver zinc zeolite was accepted in an exeptional case, but it can't be accepted the other way round.
The study *5.10.2-03 by Duan*, shows bacteriostatic effects on two gram-positive and two gram-negative bacteria on a low density polyethylene (LDPE). The loading of the material is 5% and represents the upper limit given by the applicant for incorporation into materials; the test conditions are wet. Study IIIB 5.10.2-04 shows inhibition of growth for E. coli and P. aeruginosa; for S. aureus and Listeria, however, this could not be shown. The test conditions are intermittently humid and less humid and the samples were inoculated freshly for five consecutive days. If not the average of the 5 consecutive inoculations is taken into account, but if the inoculation counts are added, then growth could not be shown for any of the organisms (see 5.10.2-04 a-d). In conclusion, test 02 and 03 are acceptable as Tier 1 test for a bacteriostatic claim for the named example application. However, disinfectants for air-conditioning systems are normally applied by airborne diffusion of an aerosol, a smoke, a vapour or a gas. It would need to be shown with appropriate tests that this function can be fulfilled even by a biocide incorporated into the parts of an air-conditioning system. To demonstrate this, a semi-field trial is required as a tier 2 test. Such a test has not been provided. In conclusion, efficacy for example-application 2 is not demonstrated.
Whether a fungistatic claim has been made, is not quite clear. The test IIIB 5.2.10-05 mentions PT2, though in the original dossier, a fungistatic claim has not been made. The test IIIB 5.10.2-05 carried out with 3 different fungal species could not demonstrate inhibition of growth. Thus, a fungistatic effect has not been demonstrated.

PT 4

Two example uses were given: i) "Polymer kitchen utensil to help maintaining a hygienic surface" and ii) "Treatment of granular activated carbon(GAC) in flow-through water filters to reduce clogging and pressure". These were later replaced by i) food packaging, ii) food containers, tubing, iii) food processing equipment, iv) food utensils." However, the first named example uses were used to evaluate the provided studies. The example applications given later are rather a collection of possible uses and are too unspecific to give an indication about use-conditions.

PT 7

For PT 7, a fungistatic claim has been made. The materials named are polymers, coatings, laminates, adhesives and sealants. The example uses given were i) laminated work surface and ii) paint finish.
For PT 7, the material and the use-conditions are a crucial factor to motivate why deterioration by fungal growth is to be expected. Hard plastic surfaces used indoors, for instance, are usually not easily colonised by fungi. Generally, use conditions need to entail a certain amount of constant humidity to make the material prone to fungal growth. Thus, materials and use-conditions should be described in more detail at least for the example uses given. Laminate does not say anything about the material, only that it consists of several different layers. For a paint-finish, however, it can be assumed that paints generally are more likely to be colonised. The release characteristics of an active/material combination should be known in order to chose the right test. Test conditions should apply represantative materials, use-conditions and organisms. Usually, consortia of organisms should be employed for testing rather rather than single species. The effects of ageing under relevant use conditions should be explored in a tier 2 test.
There have been two tests submitted which employ fungi as test organisms: The test by Foster, L. (2015) III B 5.10.2-02 and the test IIIB 5. 10.2-05 (see table under 7.1). The Foster test employs only filter paper as a control instead of an untreated sample. In case of paper as a tested material, this might be acceptable; for the tested coated fabric it is not. However, paper does not represent one of the example uses given. In test IIIB 5.10.2-05, an untreated material has been employed as a control. Nevertheless, it was not possible to show that the LDPE material supported fungal growth in the untreated samples. This is not surprising as hard plastics are not prone to fungal growth.

In reaction to eCAs comments on insufficient efficacy data, the applicant sent in the following revised data, again referring to tests carried out on silver zinc zeolite and silver copper zeolite. The tested organism was A. niger in all cases:

Zeolite type	**Zeolite loading**	**Silver loading**	**Tested material**	**Results**	**Reference**
AJ10D	5%	0.125%	Acrylic coating on aluminium	Filter paper: 4 Untreated control: 1-2 Treated sample: 0	Silver zinc zeolite, IIIB 5.10.2-04
Evidence of growth on untreated control. Complete control is achieved with a sample treated at 0.125% silver load.					
AJ10D	0.5% 1.0% 3.0% 5.0%	0.0125% 0.025% 0.075 0.125%	Coated fabric	Filter paper: = 4 0.0125% silver: = 2 0.025% silver: = 1 0.075 silver: = 0 0.125% silver: = 0	Silver zinc zeolite IIIB 5.10.2-12
Evidence of increased growth with reduced levels of silver in the article; by extrapolation untreated samples will show significant growth. Complete control is achieved with the sample treated at 0.075% silver load; good control is achieved at 0.025% silver load.					
AK10D	0.5% 1.0% 3.0% 5.0%	0.025% 0.05% 0.150 0.25%	Coated fabric	Filter paper: = 4 0.025% silver: = 2 0.05% silver: = 1 0.150 silver: = 1 0.25% silver: = 0	Silver zinc zeolite IIIB 5.10.2-12
Evidence of increased growth with reduced levels of silver in the article, an untreated sample will show substantial growth. Complete control achieved with a sample treated at 0.25% silver load, good control at 0.05% silver load.					

Zeolite type	Zeolite loading	Silver loading	Tested material	Results	Reference
--	--	--	HIPS	Filter paper: 4,4,4 Untreated control: 3,3,1	Silver zinc zeolite IIIB 5.10.2-04
--	--	--	PET fibre	Filter paper: 4 Untreated control: 4	Silver zinc zeolite IIIB 5.10.2-04
Data shows evidence of growth on untreated control matrices					

The applicant claims that the data are relevant to silver zeolite based on comparable silver release and comparable or higher silver loadings expected for silver zeolite.
The tests are not acceptable due to the reasoning given under PT 2. Furthermore, the test IIIB 5.10.2-12 has not been accepted for silver zinc zeolite due to the lack of growth on untreated controls. For the IIIB 5. 10.2-04 test, the applicant has not submitted the protocols of the tests they refer to in the table above, only summaries of results, so that e.g. growth in controls cannot be assessed. In conclusion fungistatic efficacy for an example application under PT 7 has not been demonstrated.
Whether a bacteriostatic claim has been made, is not quite clear. The tests IIIB 5.2.10-03 and -04 mention PT7, though in the original dossier, a bacteriostatic claim has not been made. Again, LDPE does not seem to be a representative material for the example uses given nor are the tested organisms representative for typical PT 7 applications.

7.2 MODE OF ACTION

Please refer to 2.3.2 in the A part of this report.

7.3 RESISTANCE

Please refer to 2.3.3 in the A part of this report.

7.4 CONCLUSION ON EFFICACY

Silver zeolite is used to treat a variety of polymer materials or articles to either prevent microbial growth when the materials or articles are used in humid/wet conditions or to protect humans from cross-contamination with pathogens (the latter claims are made for PT 2 and 4 only).

PT 2
Efficacy has not been demonstrated, neither for a fast bacteriocidal effect to prevent cross-contamination, nor for a claim of prevention of bacterial growth.

PT 4
Efficacy has not been demonstrated for a fast bacteriocidal effect to prevent cross-contamination. This is relevant for most applications in food contact material (FCM).

For the claim "prevention of bacterial growth" efficacy has been demonstrated for example applicaton 2 "Treatment of granular activated carbon(GAC) in flow-through water filters to reduce clogging and pressure". Efficacy has been demonstrated in a tier 2 simulated use test, were silver zeolite was effective to keep the microbial count in the effluent of the filter under 500 CFU/100 ml up to a flow-through of ca. 6400 l.
Conclusions on applications in static water-filters (post-tap) or conclusions on the efficacy of other food contact material where prevention of growth is claimed cannot be made. Representative examples of such applications would have to be tested specifically.

PT 7
Efficacy has not been demonstrated for a fungistatic claim for a representative use under PT 7.

8 HUMAN EXPOSURE ASSESSMENT

Intended uses PT 2, 4, 7		
Product type	**Area of use**	**Type of application**
PT2 Private area and public health area disinfect-ants	Consumer items Personal care items Ventilation, heating and conditioning parts Polymer wall or floor coatings Protective covers Sanitary items	Polymer masterbatch production Treated article use
PT4 Food and feed area disinfectants	Kitchen utensils Food containers Food packaging Water filter	Polymer masterbatch production Treated article use
PT7 Film preservatives	Polymer coatings (laminated work surface, paint finish, protective finishes applied to foam, moulded parts, rubber sheet) Adhesives Sealant	Polymer masterbatch production Treated article use

A comprehensive list of uses for silver zeolite provided by the applicant during different stages of the evaluation is found in Appendix II.

8.1 IDENTIFICATION OF MAIN PATHS OF HUMAN EXPOSURE TOWARDS ACTIVE SUBSTANCE FROM ITS USE IN BIOCIDAL PRODUCT

The applicant claims that the active substance is not manufactured in the EU or EES. After having been imported into the EU or EES, the active substance is incorporated into polymers that are later shaped into treated articles. The biocidal product is identical with the active substance.

The active substance is incorporated into polymers and coatings at a maximum level of 5.0% by weight. The active substance is incorporated into polymers at a maximum level of 0.5% by weight for use in textiles. The assessment of exposure from mixing and loading is made for the polymer formulation. According to the applicant, the textiles are not used for apparel, but the use can include bed textiles.

Formulation and shaping steps might occur in EU or EES. If a masterbatch is used in the formulation step to provide the biocidal property to the bulk polymer, it should be considered as biocidal product (see CA-Sept15-Doc.6.2 – Final).

A treated article can in general be used for many months or years. The active substance is distributed throughout the mass of the polymer that makes up the treated article. It can also be compounded into a coating, film, or laminate, which is then applied to the finished product. In any case, incorporation in a polymer matrix is involved.

The crystalline zeolite structure acts as a carrier for silver ions. Ions are released through ion exchange into electrolytic media such as sweat or saliva. Released ions migrate from the polymer matrix into the medium, the speed and amount depending on the type of medium, type of polymer and duration of contact during use. Thus, the silver ion is the main chemical form that consumers will be exposed to.

The exposure assessment for professionals workers handling silver zeolite considers handling events described as i) mixing and loading ii) packaging and transport iii) application of coatings by spray and iv) application of coatings by roll-on. These handling events have been described previously in the draft CAR for silver zinc zeolite and are relevant to silver zeolite since the two substances are used in the same manner by professionals and they contain a similar level of silver (ca 5%).

Inhalation
Industrial and professional inhalation exposure will primarily be a result of the workers handling of the active substance before,during and after the formulation of polymers, and in the application of coatings. Silver zeolite is not volatile, but due to its dustiness there is potential for inhalation of air-borne particles. Inhalation of aerosols is a possible way of exposure during spray-application of coatings. There might be some release of silver-containing particles from treated articles into air by wear and tear, but inhalation exposure possibly resulting from this is considered negligible, as well as exposure via the environment.

Dermal
Industrial and professional dermal exposure will primarily be a result of the workers handling of the active substance before,during and after the formulation of polymers, and in the application of coatings. There is potentially significant dermal exposure to silver released from treated articles by the general public. This in particular concerns articles designed to have contact with human skin such as clothes. Also, toddlers and infants will be at risk for dermal exposure if they crawl on floors being treated with the biocidal product. There will be negligible dermal contact resulting from silver released into the environment.

Oral
There is potential for oral uptake of silver from use of treated articles by the general public: Either from articles that are intended to be placed into the mouth like dental mouth guards or tooth brushes, or articles that are accidentally taken into the mouth by infants or toddlers. There is potentially oral exposure to the general public from food contact uses of the biocide such as food packaging. Oral exposure from industrial use is expected to be negligible, as well as via release into the environment.

Note: Risk characterisation for professionals is based on the biocidal product (= silver zeolite). Where it can be assumed that exposure will occur only to silver ions, the risk characterisation is based on silver ions.

For consumers, the risk assessment is based on silver ions released from the treated articles(s).

Summary table: relevant paths of human exposure							
Expo-sure path	**Primary (direct) exposure**			**Secondary (indirect) exposure**			
	Indus-trial use	**Professional use**	**Non-profes-sional use**	**Industrial use**	**Professional use**	**General public**	**Via food**
PT2 Private area and public health area disinfectants							
Inhalation	Yes	No	No	Yes	Yes	No	No
Dermal	Yes	No	No	Yes	Yes	Yes	No
Oral	No	No	No	No	No	Yes	No
PT4 Food and feed area disinfectants							
Inhalation	Yes	No	No	Yes	Yes	No	No
Dermal	Yes	No	No	Yes	Yes	Yes	No
Oral	No	No	No	No	No	Yes	Yes
PT7 Film preservatives							
Inhalation	Yes	No	No	Yes	Yes	No	No
Dermal	Yes	No	No	Yes	Yes	Yes	No
Oral	No	No	No	No	No	Yes	No

8.2 LIST OF SCENARIOS

The list below contains all scenarios for industrial, professional, non-professional and secondary exposure, but exclude dietary exposure which is covered in Chapter 8.7

Summary of scenarios				
Scenario number	**Relevant product type(s)**	**Scenario**	**Primary or secondary exposure Description of scenario**	**Exposed group** (e.g. professionals, non-professionals, bystanders)
1	2, 4, 7	Mixing/loading (incl. transport, packaging and maintenance)	Primary exposure:	Industrial workers
2	2, 7	Spray application (incl. cleaning of spraying equipment)	Secondary exposure:	Professionals
3.1	2, 7	Brush and roller application	Secondary exposure:	Professionals
3.2	2, 7	Brush and roller application	Secondary exposure:	Non-professionals
4	7	Manual application of sealants	Secondary exposure:	Professionals and non-professionals
5.1	2, 4, 7	Dermal exposure to treated polymer: direct contact with human skin	Secondary exposure: Small-scale	General public
5.2	2, 7		Secondary exposure: Medium scale	
5.3	2, 7		Secondary exposure: Large-scale	
6	2, 7	Oral exposure to treated polymer: hand-to-mouth contact	Secondary exposure: Toddler or infant crawling on floor	General public
7.1	2	Oral exposure to treated polymer: taking into mouth	Secondary exposure: Small-scale	General public
7.2			A) Large-scale for infants and toddlers B) Large-scale for children and adults	General public
8	2	Oral exposure to treated textile: taking into mouth	Secondary exposure: Textile taken into mouth by infants or toddlers	General public
9.1	2	Dermal exposure to treated textile: direct contact with human skin	Secondary exposure: Large-scale	General public
9.2			Secondary exposure: Small-scale	General public
9.3			Secondary exposure: Handling of wet textile	General public

Description of exposure categories and scales used in the risk assessment for secondary (indirect) exposure as a result of use in treated articles (chapter 12.6)

Note: In order to be approved, use in a specific treated article must be acceptable both in the corresponding dermal and oral exposure category and scale.

Exposure scenario and category		**Exposure values**	
		Surface of body expected to be covered by/in contact with the article [cm²]	*Duration of contact*
Dermal exposure to treated polymer			
5 Dermal exposure to treated polymer: direct contact with human skin under wet conditions	**5.1** Small-scale	Adult: 410 Child: 214 Toddler: 115 Infant: 98 (corresponds to both hand palms)	1 min
	5.2 Medium-scale	Adult and child: 300 Toddler and infant: 200	30 min
	5.3 Large-scale	Adult: 8300 Child: 4600 Toddler: 2400 Infant: 2050 (corresponds to 50% of the total body surface, incl. head, hands and feet; exposure assessment assumes that 70% of the polymer's surface is in direct contact with skin under wet conditions; resulting in 35% of body surface exposed)	3h
Oral exposure to treated polymer			
6 Oral exposure to treated polymer: hand-to-mouth contact	Toddler or infant crawling on floor	Toddler: 115 Infant: 98 (corresponds to both hand palms; exposure assessment assumes that 40% of the polymer's surface is in direct contact with palms under wet conditions, and 50% of the substance is transferred from hand to mouth)	1h
7 Oral exposure to treated polymer: taking into mouth	**7.1** Small-scale	Adult and child: 62.8 Toddler: 31.4	5 min
	7.2 A) Large-scale for infants and toddlers	Toddler and infant: 12.6	Toddler: 1.4h Infant: 4.75h
	7.2 B) Large-scale for children and adults	Adult and child: 20	8h
Oral exposure to treated textile			
8 Oral exposure to treated textile: taking into mouth	Textile taken into mouth by infants or toddlers	Weight of article (or parts of articles expected to be taken into mouth: Toddler and infant: 1.3 g	Toddler: 1.4h Infant: 4.75h
Dermal exposure to treated textile			
9 Dermal exposure to treated textile: direct contact with human skin under wet conditions	**9.1** Large-scale	Adult: 13540 Child: 7636 Toddler: 3878 Infant: 3313 (corresponds to the total body surface except head, hands and feet) (exposure assessment assumes that 70% of the textile's surface is in direct contact with skin)	8h-24*
	9.2 Small-scale	Adult: 1130 Child: 605	8h-24*

Exposure scenario and category		Exposure values	
		Surface of body expected to be covered by/in contact with the article [cm²]	*Duration of contact*
		Toddler: 288 Infant: 246 (corresponds to surface of both feet) (exposure assessment assumes that 70% of the textile's surface is in direct contact with skin)	
	9.3 Textile handling	Adult: 410 Child: 214 Toddler: 115 (corresponds to both hand palms)	2h

* The present report contains contradicting information about the duration – 8h and 24h. The 8h was initially used for the calculation (appendix II), whereas 24h was mentioned as worst-case in the descriptions of the scenarios elsewhere in the document. This discrepancy did not influence the conclusions of the risk assessment, since the available migration data showed that silver migration has decreased to a very low rate already after 2h. Therefore, the duration did not gain further attention during the evaluation.

Summary of dietary exposure scenarios (see chapter 8.7.1)			
Scenario number	**Type of use**	**Description of scenario**	**Subject of exposure**
D1	Food contact materials	Migration from polymers into food	General public
D2	Preservation of water filter	Silver ions released into drinking water (see chapter 8.7.5)	General public

8.3 INDUSTRIAL EXPOSURE

PT 2, 4, and 7

The information given by the applicant regarding details of procedures and facilities when mixing and loading the active substance during polymer formulation is very limited.

The exposure assessment for professionals workers handling silver zeolite considered handling events described as i) mixing and loading ii) packaging and transport iii) application of coatings by spray and iv) application of coatings by roll-on. These handling events have been described previously in the draft CAR for silver zinc zeolite and are relevant to silver zeolite since the two substances are used in the same manner by professionals and they contain a similar level of silver (ca 5%).

8.3.1 Scenario 1 - Mixing and loading (incl. transport, packaging and maintenance).

The assessment of exposure from mixing and loading is made for the polymer formulation.
The RISKOFDERM model is used for dermal exposure. Initially, in the first draft CAR for silver zinc zeolite, the TNsG model was used for inhalation exposure. As response to comment received during the peer review of silver zinc zeolite, we proposed to use the MEASE model. The point was closed and never discussed at TMII 2013. Later, during peer review of silver sodium hydrogen phosphate and two other silver compounds, we received the

comment that we should use the TNsG model and agreed to do so. Generally, the applicability of MEASE for this type of substance was questioned, but not specifically the use for mixing and loading. Therefore, we are presenting exposure assessments using both the TNsG model and the MEASE model in this updated version of the CAR.

Exposure during packaging and transport will be to the resulting incorporated product, either masterbatch or coating formulation. The product will be either a viscous liquid or a macro sized solid, such as a masterbatch polymer. Exposure during transport and packaging is expected to be less than during the mixing and loading phase.
In recent substance evaluations (namely tolylfluanid and fludioxonil) additional exposure from the task of maintenance of machines has been assessed. Again, like for transport and packaging, the exposure will be to the formulated polymer and consequently the exposure to the active substance will be lower than during mixing and loading. Given the extremely limited information about the formulation processes in general, we believe it is covered by the conservativeness of the defaults for the mixing and loading steps.

Details of calculations are found in Appendix II.

Primary exposure – Dermal			
	Parameters	**Value**	**Reference**
Tier 1	Exposure loading per shift hands	225 mg	RISKOFDERM model output
	Content of the active substance in the formulation	5 %	
	Exposure of workers hands	11.25 mg/d	
	Dermal absorption of product	5%	
	Operator body weight	60 kg	
	Systemic exposure to product	**0.0094 mg/kg bw per day**	
Tier 2	Reduction due to use of protective gloves	95%	
	Systemic exposure to product	**0.00047 mg/kg bw per day**	

Primary exposure – Inhalation - MEASE model			
	Parameters	**Value**	**Reference**
Tier 1	Inhalation exposure estimate	5 mg/m³	MEASE model output
	Inhalation rate	1.25 m^3/h	Vol. III Part B default
	Content of the active substance in the formulation	5 %	
	Inhalation absorption of product	100%	
	Duration and frequency of task	10 min, one operation per day	applicant
	Potential inhalation exposure	0.52 mg/d	
	Operator body weight	60 kg	
	Systemic exposure to product	**0.0087 mg/kg bw per day**	
Tier 2	Reduction due to use of respiratory protection	95%	
	Systemic exposure to product	**0.00043 mg/kg bw per day**	

Primary exposure – Inhalation – TNsG model 5				
	Parameters	**Value**	**Unit**	**Reference**
Tier 1	Workers body weight	60	kg	TNsG
	Amount handled per day	10	kg	applicant
	Content of the active substance in the formulation	5	%	
	Inhalation absorption	100	%	
	Indicative exposures	0.66	mg/kg a.s.	TNsG Model 5: Professional pouring formulation from a container into a fixed receiving vessel e.g. reservoir tank on tractor.
	Total potential inhalation exposure per day	0.33	mg	indicative exposure value x amount handled
	Systemic exposure to product	**0.0055**	mg/kg bw per day	Total potential inhalation exposure per day / body weight
Tier 2	Reduction due to use of respiratory protection	95	%	
	Systemic exposure to product	**0.000275**	mg/kg bw per day	

Summary table: systemic exposure from industrial uses				
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated total uptake**
Scenario 1 mixing and loading	Tier 1	MEASE: 0.0087 mg/kg bw per day TNsG model 5: 0.0055 mg/kg bw per day	0.0094 mg/kg bw per day	0.018 mg/kg bw per day 0.015 mg/kg bw per day
	Tier 2 Respiratory protection (95%)	MEASE: 0.00043 mg/kg bw per day TNsG model 5: 0.000275 mg/kg bw per day	0.0094 mg/kg bw per day	0.0098 mg/kg bw per day 0.0097 mg/kg bw per day
	Tier 2 Protective gloves (95%)	MEASE: 0.0087 mg/kg bw per day TNsG model 5: 0.0055 mg/kg bw per day	0.00047 mg/kg bw per day	0.00915 mg/kg bw per day 0.00597 mg/kg bw per day
	Tier 2 Respiratory protection (95%) and protective gloves (95%)	MEASE: 0.00043 mg/kg bw per day TNsG model 5: 0.000275 mg/kg bw per day	0.00047 mg/kg bw per day	0.00090 mg/kg bw per day 0.00075 mg/kg bw per day

8.4 PROFESSIONAL EXPOSURE

PT 2

Professionals may become exposed when applying formulated paints onto walls or floors by brushing, rolling or spraying. According to the applicant, spray coating is an automated process where workers are excluded. Furthermore, professionals may be exposed to the active substance from handling treated articles during activities like installation, transport or packaging. These activities are covered by the consumer exposure scenarios.

PT 4

Professionals are not expected to be exposed to the active substance other than from handling the treated articles during activities like installation, transport or packaging. These activities are covered by the consumer exposure scenarios.

PT 7

Professionals may become exposed when applying formulated paints onto walls or floors by brushing, rolling or spraying. According to the applicant, spray coating is an automated process where workers are excluded.
Professionals may become exposed when applying formulated sealants by hand. Furthermore, professionals may be exposed to the active substance from handling treated articles during activities like installation, transport or packaging. These activities are covered by the consumer exposure scenarios.

8.4.1 Scenario 2 - Spray application (incl. cleaning of spraying equipment)

The WG-V 2017 agreed that the standard models for antifouling paints and spraying according to TNsG should be used. Therefore, the eCA recalculate the exposure using the Spraying Model 3 for antifouling paints, replacing the previously applied MEASE model.

The applicant has not provided further information about the way of spray application or about the type of protective equipment used.

In recent substance evaluations (namely tolylfluanid and fludioxonil) additional exposure from the task of cleaning of spraying equipment has been assessed. Given the extremely limited information about the paint or coating application in general, we believe it is covered by the conservativeness of the defaults for the spray application steps.

Details of calculations are found in Appendix II.

Secondary exposure – Dermal				
	Parameters	**Value**	**Unit**	**Reference**
	Dermal absorption	5	%	
	Operator body weight	60	kg	
Tier 1	Total dermal deposit of product	3321	mg/d	Professional spraying, Spraying model 3
	Systemic exposure to product	2.77	mg/(kg bw * d)	
Tier 2	Total dermal deposit of product	131	mg/d	Hands inside gloves and body protected with overall (95% protection)
	Systemic exposure to product	0.109	mg/(kg bw * d)	

Secondary exposure – Inhalation				
	Parameters	**Value**	**Unit**	**Reference**
	Inhalation absorption	100	%	
	Operator body weight	60	kg	
Tier 1	Inhalation exposure estimate of product	3	mg/d	Professional spraying, Spraying model 3
	Systemic exposure to product	0.05	mg/(kg bw * d)	
Tier 2	Inhalation exposure estimate of product, 95% reduction due to use of respiratory protection	0.16	mg/d	95% reduction due to use of respiratory protection

	Systemic exposure to product	0.003	mg/(kg bw * d)	

8.4.2 Scenario 3.1 - Brush and roller application by professionals

Application of coatings by spraying or roll on is an industrial or non-industrial process where workers can become exposed to the active substance.

The WG-V 2017 agreed that the HEEG Opinion 15 should be used in the exposure assessment of brush and roller painting for professionals, replacing the previously applied CONSEXPO and MEASE models.

The applicant has not provided further information about the way of brush or roller application or about the type of protective equipment used.

The HEEG opinion distinguishes between application mainly by brushing or mainly by rolling. Two different models are proposed for professionals depending on whether brushing or rolling is the dominating activity. The applicant has not provided any such information. In any case, tier 1 will result in very high unacceptable risk. Thus, we use the scenario that results in the highest exposure in tier 2, which would be the Consumer product painting model 4 acc. to HEEG opinion 15 (higher total exposure due to higher amount inside gloves when compared the Links study). Furthermore, HEEG opinion 15 mentions brushing and brushing/rolling, therefore, both way of application are hereby included.

We use an exposure duration of 7h and do not consider inhalation exposure, no aerosols are formed and the active is not volatile (in line with recommendations for PT 7 in the Exposure methodology manual). We use a 95% reduction of body exposure for tier 2 (impermeable coverall, in line with HEEG opinion 9).

In recent substance evaluations (namely tolylfluanid and fludioxonil) additional exposure from the task of cleaning of spraying equipment has been assessed. Given the extremely limited information about the paint or coating application in general, we believe it is covered by the conservativeness of the defaults for the application steps.

Secondary exposure – Dermal				
	Parameters	**Value**	**Unit**	**Reference**
	Dermal absorption	5	%	
	Operator body weight	60	kg	
Tier 1	Total dermal deposit of product	483	mg/d	Consumer product painting model 4, HEEG opinion 15
	Systemic exposure to product	0.40	mg/(kg bw * d)	
Tier 2	Total dermal deposit of product	90	mg/d	Hands inside gloves and 95% body exposure reduction using impermeable coverall
	Systemic exposure to product	0.08	mg/(kg bw * d)	

Details of calculations are found in Appendix II.

8.4.3 Scenario 4 - Manual application of sealants

[*Remark: the following scenario has been added by the eCA. It has not been part of the agreed scenarios for silver zinc zeolite*]

The CONSEXPO model, modified for professional users, is used for dermal exposure. Inhalation exposure is not relevant, since the active substance is not volatile

CONSEXPO contains defaults for the tasks painting by spraying and by brush and roller. No information has been provided by the applicant regarding details of how sealants are applied by professionals. Therefore, we applied the CONSEXPO defaults, except for the values shown in the table above. Duration of the task was adjusted to 300 min in order to reflect a professional working with this task during a great part of a work shift.

A higher tier assessment is based on the assumption that silver will be limited by the migration rate from the sealant similarly to the scenarios for consumer exposure. In this case, the exposure to silver ions, not the whole active substance will be estimated.

Details of calculations are found in Appendix II.

Secondary exposure – Dermal			
	Parameters	**Value**	**Reference**
Tier 1	Dermal external dose per work shift	750 mg/kg bw	CONSEXPO output
	Dermal absorption of product	5%	
	Operator body weight	60 kg	
	Systemic exposure to active substance	**0.625 mg/kg bw per day**	
Tier 2	Dermal external dose	6.56 µg silver ions	
	Dermal absorption of silver	5%	
	Operator body weight	60 kg	
	Systemic exposure to active substance	**0.005 µg/(kg*day) silver ions**	

8.4.4 Summary of professional exposure

Summary table: systemic exposure from professional uses				
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake [mg/(kg bw * day)]**	**Estimated dermal uptake [mg/(kg bw * day)]**	**Estimated total uptake [mg/(kg bw * day)]**
Scenario 2 – spray application	Tier 1	0.05	2.77	2.82
	Tier 2 Hands inside gloves and body protected with overall (95% protection), 95% reduction due to use of respiratory protection	0.003	0.109	0.11
Scenario 3.1 – brush and roll application	Tier 1	-	0.40	0.40
	Tier 2 Hands inside gloves and 95% body exposure reduction using impermeable coverall	-	0.075	0.075
Scenario 4 – joint sealant application	Tier 1	-	0.625	0.625
	Tier 2 Silver migration rate	-	0.005 µg/(kg*day) silver ions	0.005 µg/(kg*day) silver ions

8.5 NON-PROFESSIONAL EXPOSURE

The application of wall or floor paint by non-professionals has not been explicitly mentioned by the applicant, but neither has it been excluded. Spray application is always an automated industrial process, but application by brushing and rolling might be relevant for non-professionals. The manual application of sealants by non-professionals is covered by the scenario for professionals, since all input values are the same for professionals and non-professionals.

8.5.1 Scenario 3.2 - Brush and roller application by non-professionals

The CONSEXPO scenario for brush/roller painting of waterborne wall paint is used. As for professionals, inhalation exposure is not expected.

Details of calculations are found in Appendix II.

Secondary exposure – Dermal			
	Parameters	**Value**	**Reference**
Tier 1	Dermal external dose per application	180 mg	CONSEXPO output
	Dermal absorption of product	5%	
	Operator body weight	60 kg	
	Systemic exposure to product	**0.15 mg/kg bw per day**	

During peer review, the German eCA made the comment that has unfortunately not been taken up in the Working Group (WG V 2017) discussion:

> Please revise the non-professional exposure scenario for brush and roller application using the Model "Brushing sheds and fences, outdoor (direct from can)" (Biocides Human Health Methodology document (215), In-situ application of wood preservatives with brush, p. 216) for outdoor applications. In case indoor application is possible please use the model "Rough wooden joists and the underside of floor boards, overhead indoors, with water based product".
>
> Justification: For dermal exposure calculation the eCA used ConsExpo. Normally, the above mentioned models are used.
> For inhalation exposure, the MEASE model is used by the eCA. This model is considered not applicable due to the following reasons:
> - It is a model for professional use;
> - Data used for model development are not given and therefore are not comprehensible.
>
> The above mentioned models provide exposure data for dermal exposure (body and hands) and inhalation exposure for non-professionals (outdoor or indoor).

We have assessed the exposure resulting from the mentioned models and no change in the outcome of the risk assessment would result from them; therefore, the German authority agreed not to recalculate the scenarios at this point in time, but take this into account in the coming evaluations of silver substances and at product authorisation.

8.6 SECONDARY EXPOSURE OF THE GENERAL PUBLIC EXCLUDING DIETARY EXPOSURE

Note: Risk characterisation for the general public is based on <u>silver ions</u> as the active chemical entity.

The migration rate, i.e. the speed with which the silver ions migrate out of the treated material, is the crucial parameter for exposure estimates. It is more important than the actual silver concentration in the polymer matrix. Furthermore, the polymer properties, in particular the ability to absorb water, are expected to have influence on the migration speed (see chapter 9).

One study with another silver containing zeolite with LDPE was provided. The applicant conducted migration studies with silver zinc zeolite. The migration of silver ions treated within silver zinc zeolite migrating from ABS, PC, LDPE, PP coupon into artificial body fluids was measured in the provided studies. Additionally, or PET fibrous material immersed in artificial body fluids for 2 hours and for 24 hours at 37°C, simulating long-term and short-term contact times, was investigated with silver copper zeolite. The applicant provided one

study in which migration of silver from 3 samples of treated fibres into body fluids was investigated, but no study with silver zeolite and textiles.

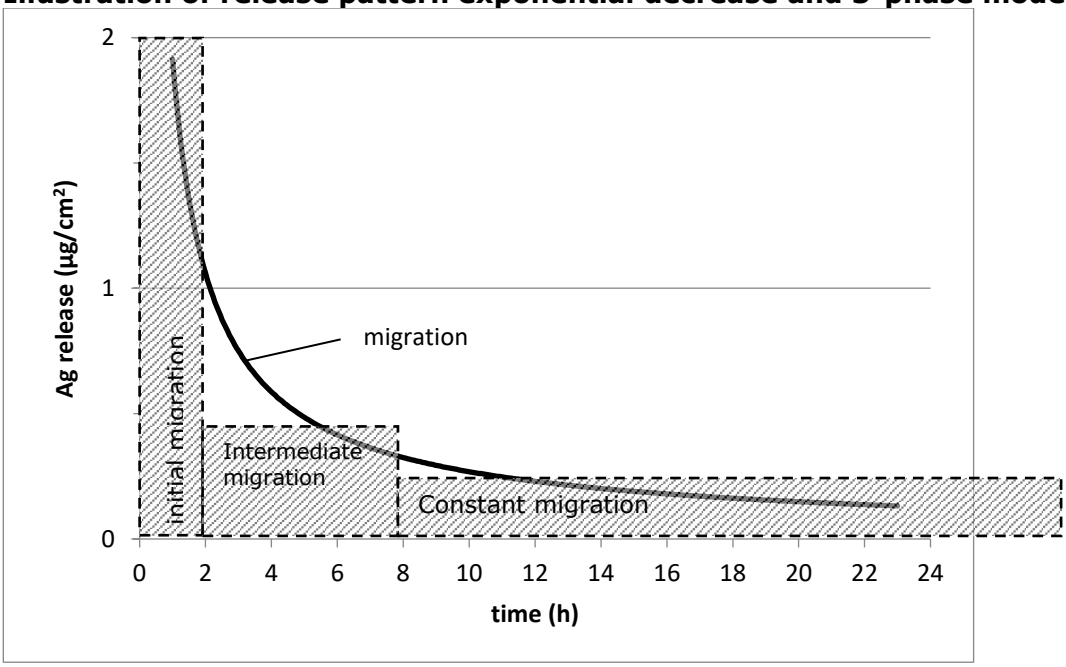
All study results mentioned with the different zeolite types are listed in Appendix II.

The test media simulating body fluids were:

1. Artificial human sweat (acid, pH 5.5)
2. Artificial human sweat (alkaline, pH 8.0)
3. Artificial human saliva (neutral, pH 6.8)

Available migration studies with silver zinc zeolite show that the migration rate is much higher initially and subsequently decreasing. The decrease is likely exponential, but data are not sufficient to calculate the equation. For practical reasons, the migration pattern is divided into three phases: an initial high migration followed by an intermediate migration rate and finally a constant slow migration rate. (see figure below). As a default, an initial migration rate during hours 0-2, an intermediate migration rate of for hours 2-8h and a constant migration rate for exposure duration beyond 8 hours are assumed in all exposure scenarios from treated polymer articles. The intermediate migration rate was calculated as the geometric mean of the two measured migration rates.
The migration will differ substantially between materials and conditions (for more information see chapter 8.7 and 9). The polymers used, their physical properties and composition are not specified for the described uses. To overcome these uncertainties, migration measurements reflecting real exposure situation would need to be generated.

Illustration of release pattern exponential decrease and 3-phase model



Migration rates – polymers

The available migration studies with silver zeolite and silver zinc zeolite show that

- migration rates may vary up to a factor of 5 between different polymers, whereby ABS showing the highest migration rates
- migration is about 4 times higher from LDPE treated with silver zeolite than for the same polymer treated with silver zinc zeolite.

Therefore, we use the migration study with silver zeolite together with a safety factor of 2 in order to estimate migration rates used in this evaluation. This factor is chosen since only LDPE was tested. Variation among polymers within factor 5 for silver zinc zeolite and LDPE in the upper half of the migration ranges for non-porous polymers tested with silver zinc zeolite.

Migration rates of silver from polymers used for exposure scenarios

Dermal (migration into sweat)

	Silver zeolite	Silver zeolite (safety factor: 2)	
MR initial = initial release phase (0- 2h)	65.6	131	ng * cm^{-2} x h^{-1}
MR intermediate = geometric mean release (2h-8h)	15.9	32	
MR constant = release rate after 8h and onward	3.86	7.7	

Oral (migration into saliva)

	Silver zeolite	Silver zeolite (safety factor: 2)	
MR initial = initial release phase (0- 2h)	65.6	131	ng * cm^{-2} x h^{-1}
MR intermediate = geometric mean release (2h-8h)	15.2	30	
MR constant = release rate after 8h and onward	3.51	7.0	

Migration rates - textiles

Silver migration data for textiles are not available for silver zeolite. The uncertainty in extrapolation is addressed by applying a safety factor (x 10) to the available silver copper zeolite migration data from treated textiles.

The SCZ treated PET fibre study used a textile sample containing and LDPE surface finish treated with 1.5% SCZ, and an unspecified textile treated with 0.34% SCZ. According to the applicant, the fibres were manufactured via a compounding process where the silver copper zeolite is embedded into the fibre. The sample with 0.34% displays a more rapid migration. The applicant states that they do not have control of the process the SCZ was incorporated in the fibre. Since it represents a realistic textile sample, as it could be found on the EU-market, we use this sample for the exposure assessment.

The applicant provided also migration data from a topically treated fabric. We did not use the data derived with the third sample because the treatment is a combination of both silver zinc zeolite (Tye AJ) and silver copper zeolite (type AC). Furthermore, the application process is not in line with those described in the dossier (i.e. incorporation into polymer

matrix) and because the content of the active substances in the sample is not known (information lacking on amount of slurry attached to fibres after treatment, and on weight of textile sample). The measured released silver might well be in the form of the active substance, i.e. the silver copper or zinc zeolite detached from the fibre, rather than the dissolved silver ions. However, the data indicate that migration of silver from topically treated textiles might be very rapid.

In the case of textiles, migration rates based on surface area are not applicable because this needs assumptions about the surface that comes into contact with sweat or saliva. For a fibrous material, however, the surface can be virtually infinite. It is more appropriate to relate the release to the weight of the textile worn per body surface area.

Migration rates of silver from textiles used for exposure scenarios
Migration rates for textiles are presented in percent of silver released, related to the total silver content in the tested textile material.

Dermal (migration into sweat)

	Silver copper zeolite		Silver zeolite (safety factor: 10)		
	Textile sample 1.5%	Textile sample 0.34%	Textile sample 1.5%	Textile sample 0.34%	
MR initial = initial release phase (0- 2h)	0.0052	1.11	0.052	11.1	% x h^{-1}
MR 24 = release over 24h	0.0011	0.24	0.011	2.4	
MR constant = release rate after 8h and onward	0.00022	0.051	0.0022	0.51	
MR 24 = release over 24h	0.015	3.34	0.15	33.4	%

Oral (migration into saliva)

	Silver copper zeolite		Silver zeolite (safety factor: 10)		
	Textile sample 1.5%	Textile sample 0.34%	Textile sample 1.5%	Textile sample 0.34%	
MR initial = initial release phase (0- 2h)	0.0047	1.04	0.047	10.4	% x h^{-1}
MR intermediate = geometric mean release (2h-8h)	0.0035	0.16	0.035	1.6	
MR constant = release rate after 8h and onward	0.0026	0.025	0.026	0.25	

8.6.1 Scenarios 5 - 9

The scenarios presented below are aiming to cover the great variety of uses of treated polymer articles. It is not possible to assess all imaginable kinds of articles. Therefore, we suggest exposure categories (similarly to use categories applied for wood treatment). The presented example articles are meant to represent a characteristic reasonable worst case within a use category.
This concept in general has already been agreed on for silver zinc zeolite by the TM IV 2013, including the exposure categories. The concept presented here was slightly amended, by adding a small scale category for textiles, and by making it more clear that the scenarios are categories, not specific treated articles.

Examples of use situations that will probably give rise to the highest exposure are selected as representative scenarios. The scenarios do not necessarily represent actual uses of silver zeolite but are provided to give an indication of the potential risk to human health. Infants, toddlers, children and adults differ in their behaviour and in their body weight and dimensions and separate estimates are made for these sub-populations. Where available model input parameters are selected according to the Biocides Human Health Exposure Methodology (version 1, October 2015).

8.6.2 Scenario 5 - Dermal exposure to treated polymer: direct contact with human skin

Description of Scenario 5 ***Dermal exposure to treated polymer: direct contact with human skin***		
	Parameters	**Value [µg * kg^{-1} * day^{-1}]**
Tier 1	A worst-case exposure estimate could be made based on the assumption that 100% of the silver is released from the treated article during use. For this, assumptions need to be made about the articles total weight, which in turn needs information about the article's dimensions (i.e. thickness) and the material's density. Such information is not available, and if available it would be highly variable.	
Tier 2	**5.1** Small-scale 1 min contact time Both hand palms exposed	Acute/repeated Adult:0.014 Child: 0.020 Toddler: 0.025 Infant: 0.027
	5.2 Medium scale 30 min contact time Exposed body surface 300 cm^2	Acute Adult: 0.33 Child: 0.82 Toddler: 1.31 Infant: 1.64 Repeated Adult: 0.019 Child: 0.048 Toddler: 0.077 Infant: 0.096
	5.3 Large-scale 3h contact time Exposed body surface 35% of total body surface	Acute Adult: 28 Child: 40 Toddler: 49 Infant: 52 Repeated Adult: 2.2 Child: 3.1 Toddler: 3.9 Infant: 4.2

5.1 small scale

Kitchen tops or door handles are examples for short-term dermal contact with a daily life product. Contact occurs only with inner part of hands and is in the range of a few seconds to one minute per day. The estimate is based on the assumption that a person is touching a surface with both hands for one minute.

For the acute exposure estimate the eCA assumes that this is the first time the surface is touched, i.e. the default initial migration rate applies. As a worst-case assumption for repeated exposure it is assumed that different spots of the surface are touched during different events and that surface is not cleaned or washed.

5.2 medium scale

Toilet seat is chosen as example for intermediate dermal contact with a daily life product. Contact with human skin occurs but is intermediate and only a small part of the body has contact with the article. The estimate is based on the assumption that a person is sitting on a toilet seat a certain amount of time.

For the acute exposure estimate it is assumed that this is the first time the article is used, i.e. the default initial migration rate applies. The repeated exposure estimates assume that that the same article is used at repeated occasions following the first day.

5.3 large scale

Plastic bathing mattress is chosen as a worst case example for dermal contact (Dermal contact to textiles is dealt with in a separate chapter). The estimate is based on assumption that a person is laying on a soft plastic surface. Similar exposure could occur from a foam mattress or similar. The worst case assumption in connection with bathing mattress is the direct contact between material and skin, i.e. no clothing is worn. It is furthermore assumed that the contact time is three hours and that 70% of half of the body surface is in contact with the material (contact factor 0.7).
For the acute exposure estimate it is assumed that this is the first time the mattress is used, i.e. the default initial migration rate applies for the first two hours of use, and intermediate migration rate for the following hours. The repeated exposure estimates assume that that the same mattress is used at repeated occasions following the first time use.

Details of calculations are found in Appendix II.

8.6.3 Scenario 6 - Oral exposure to treated polymer: hand-to-mouth contact

Description of Scenario 6 ***Oral exposure to treated polymer: hand-to-mouth contact***		
	Parameters	**Value [µg * kg^{-1} * day^{-1}]**
Tier 1	A worst-case exposure estimate could be made based on the assumption that 100% of the silver is released from the treated article during use. For this, assumptions need to be made about the articles total weight, which in turn needs information about the article's dimensions and the material's density. Such information is not available, and if available it would be be highly variable.	
Tier 2	Toddler or infant crawling on floor 1h contact time Exposed surface area - toddler: 115 cm^2 - infant: 98 cm^2	Acute: Toddler: 0.302 µg * kg^{-1} * day^{-1} Infant: 0.321 µg * kg^{-1} * day^{-1} Repeated: Toddler: 0.018 µg * kg^{-1} * day^{-1} Infant: 0.019 µg * kg^{-1} * day^{-1}

The estimate is based on the assumption that a toddler or infant is crawling on a floor made from hard plastic and licks its hands after contact with the treated floor. It is assumed that the children's hands are wet and that silver ions migrate from the treaded surface onto the wet hand. The WG V 2017 agreed that the parameters for dried paints as recommended for antifouling paints for hand contact[20] should be used and agreed to use 50% transfer coefficient for hand to mouth transfer, and 40% of hand surface in contact with paint. CONSEXPO defaults for duration children crawling on carpet are used. For the acute exposure estimate it is assumed that the floor is new, i.e. the default initial migration rate applies. The repeated exposure estimates assume that that the floor has been used and cleaned several times, and the migration rate is constant.

20 Recommendation 5 of the BPC Ad hoc Working Group on Human Exposure, Non-professional use of antifouling paints

Details of calculations are found in Appendix II.

8.6.4 Scenario 7 - Oral exposure to treated polymer: taking into mouth

Description of Scenario 7 Oral exposure to treated polymer: taking into mouth		
	Parameters[1]	**Value [µg * kg^{-1} * day^{-1}]**
Tier 1	A worst-case exposure estimate could be made based on the assumption that 100% of the silver is released from the treated article during use. For this, assumptions need to be made about the articles total weight, which in turn needs information about the article's dimensions and the material's density. Such information is not available, and if available it would be highly variable.	
Tier 2	**8.1** Small-scale 5 min contact time Exposed surface area 63 cm^2	Acute Adult: 0.011 Child: 0.029 Toddler: 0.034 Repeated Adult: 0.0006 Child: 0.0008 Toddler: 0.0018
	8.2 A) Large-scale for infants and toddlers 4,75h contact time Exposed surface area 12.6 cm^2 B) Large-scale for children and adults 8h contact time Exposed surface area 20 cm^2	A) acute Toddler: 0.31 Infant: 0.54 B) acute Adult: 0.15 Child: 0.37 A) repeated Toddler: 0.012 Infant: 0.052 B) repeated Adult: 0.0.019 Child: 0.047

7.1 small scale
The estimate is based on the assumption that a person (toddler, child, adult) brushes his or her teeth twice a day, 2.5 minutes each time. We estimate the surface of silver-treated bristles to 63 cm^2 (1000 bristles with a length of 1 cm and diameter of 0.2 mm). For toddlers, a toothbrush of half the size of adults is assumed.
It is assumed that this is the first time the toothbrush is used, i.e. the default initial migration rate applies. The long-term estimates assume that that the silver-treated toothbrush is used every day following the first day.

7.2 large-scale A) pacifier
The acute exposure estimate is based on the assumption that a toddler or an infant is sucking on a pacifier a certain amount of time during one day. The eCA assumes that the pacifier has a surface area of 12.6 cm^2, corresponding to a sphere of 2cm diameter. It is assumed that this is the first time the pacifier is mouthed, i.e. the default initial release rate applies for the first two hours of sucking. The repeated exposure estimate assumes

that a toddler or an infant are sucking on a pacifier a certain amount of time every day following the first day.

7.2 large-scale, B) mouthguard
The estimate is based on the assumption that a person uses a dental mouthguard during 8h per day (or night). The surface area is approximately 20 cm^2. For the acute exposure estimate it is assumed that this is the first time the mouthguard is used, i.e. the default initial migration rate applies for the first two hours of use, and intermediate migration rate for the following hours. The repeated exposure estimates assume that that the same mouthguard is used every day following the first day.

Details of calculations are found in Appendix II.

8.6.5 Scenario 8 - Oral exposure to treated textile: taking into mouth

Description of Scenario 8 Oral exposure to treated textile: taking into mouth	
Parameters	**Value [µg * kg^{-1} * day^{-1}]**
Textile taken into mouth by infants or toddlers, weighing 1.3g	Acute/repeated Toddler: 1.2 Infant: 0.53

The estimate is based on the assumption that a toddler or an infant takes a piece of textile into its mouth a certain amount of time during one day. Examples for this scenario are cuddly toys, sleeping dress or bed linen.
Migration rates based on surface area are not applicable because this needs assumptions about the surface that comes into contact with saliva. In a fibrous material, the ratio contact surface/weight can be virtually infinite. Therefore the estimate is based on the percentage of total silver contained in the textile released into saliva during one event.
For the duration of exposure we chose the same values as used in the pacifier scenario. Furthermore, it is assumed that a toddler or infant can take a piece of textile in its mouth that weighs 1.3g.

Details of calculations are found in Appendix II.

8.6.6 Scenario 9 - Dermal exposure to treated textile: direct contact with human skin

According to the applicant, use of the product/active substance in apparel is not intended, but the use can include bed textiles. Therefore, large scale explore of humans to treated textiles is not expected. Still, some exposure might occur from occasional contact with treated textiles. Therefore, the small-scale scenario is presented here that was applied for other silver-containing zeolites. Since this scenario resulted in unacceptable risk, a scenario for handling of textile items is calculated in addition.

Description of Scenario 9 ***Dermal exposure to treated textile: direct contact with human skin***	
Parameters	**Value [µg * kg^{-1} * day^{-1}]**
9.2 Small-scale 8h contact time Exposed body surface: 70% of both feet	Acute Adult: 19.8 Child: 26.6 Toddler: 30.3 Infant: 32.4 Repeated Adult: 2.4 Child: 3.3 Toddler: 3.7 Infant: 4.0
9.3 Textile handling	Acute/repeated Adult: 6.8 Child: 8.9 Toddler: 11.5

9.2 – small-scale

The estimate is based on the assumption that a person wears socks treated with the biocidal product. The release from textile can be facilitated through sweat. Thus, the exposure scenario is a worst case scenario assuming that the contact textile to skin occurs under a wet condition.
It is assumed that the feet are covered, and that 70% of this surface is in contact with the textile (default contact factor 0.7 according to CONSEXPO).

9.3 – textile handling

Remark: This scenario was added specifically for this active substance, because the small-scale scenario resulted in unacceptable risk.

The estimate is based on the assumption that a person handles textile items treated with the biocidal product. The release from textile can be facilitated through sweat. Thus, the exposure scenario is a worst case scenario assuming that the contact textile to skin occurs under a wet condition. The migration test provided by the applicant demonstrates that the major amount of silver was released during the first two hours.
The average specific weight of the fabric is assumed to be 180g/m^2.

For the acute exposure estimate the eCA assumes that this is the first time the surface is touched, i.e. the default initial migration rate applies. As a worst-case assumption for repeated exposure it is assumed that different spots of the surface are touched during different events

Details of calculations are found in Appendix II.

8.6.7 Summary of scenarios 5 - 9

Summary table: systemic secondary exposure of the general public - acute						
Dermal absorption: 5% **Oral absorption: 5%**						
Exposure scenario			**Tier/ PPE**	**Estimated dermal uptake**	**Estimated oral uptake**	**Estimated total uptake**
				µg * kg^{-1} * day^{-1}		
5. Dermal exposure to treated polymer: direct contact with human skin	5.1 Small-scale	Adult	2	0.00075		0.0007
		Child	2	0.00098		0.0010
		Toddler	2	0.00126		0.0013
		Infant	2	0.00134		0.00134
	5.2 Medium scale	Adult	2	0.016		0.016
		Child	2	0.041		0.041
		Toddler	2	0.066		0.066
		Infant	2	0.082		0.082
	5.3 Large-scale	Adult	2	1.4		1.4
		Child	2	2.0		2.0
		Toddler	2	2.5		2.5
		Infant	2	2.6		2.6
6. Oral exposure to treated polymer: hand-to-mouth contact	Toddler or infant crawling on floor	Toddler	2		0.015	0.015
		Infant	2		0.016	0.016
7. Oral exposure to treated polymer: taking into mouth	7.1 Small-scale	Adult	2		0.0006	0.0006
		Child	2		0.0014	0.0014
		Toddler	2		0.0017	0.0017
	7.2 A) Large-scale for infants and toddlers	Toddler	2		0.015	0.015
		Infant	2		0.027	0.027
	7.2 B) Large-scale for children and adults	Adult	2		0.007	0.007
		Child	2		0.019	0.019
8. Oral exposure to treated textile: taking into mouth	Textile taken into mouth by infants or toddlers	Toddler	2		0.062	0.062
		Infant	2		0.027	0.027
9.1 Dermal exposure to treated textile: direct contact with human skin	9.2 Small-scale	Adult	2	10		10
		Child	2	13		13
		Toddler	2	15		15
		Infant	2	16		16
	9.3 Textile hand contact	Adult	2	3.4		3.4
		Child	2	4.5		4.5
		Toddler	2	5.7		5.7

Summary table: systemic secondary exposure of the general public - repeated						
Dermal absorption: 5% Oral absorption: 5%						
Exposure scenario			**Tier/ PPE**	**Estimated dermal uptake**	**Estimated oral uptake**	**Estimated total uptake**
				µg * kg^{-1} * day^{-1}		
5. Dermal exposure to treated polymer: direct contact with human skin	5.1 Small-scale	Adult	2	0.00075		0.00075
		Child	2	0.00098		0.00098
		Toddler	2	0.00126		0.00126
		Infant	2	0.00134		0.00134
	5.2 Medium scale	Adult	2	0.0010		0.0010
		Child	2	0.0024		0.0024
		Toddler	2	0.0039		0.0039
		Infant	2	0.0048		0.0048
	5.3 Large-scale	Adult	2	0.112		0.112
		Child	2	0.156		0.156
		Toddler	2	0.194		0.194
		Infant	2	0.208		0.208
6. Oral exposure to treated polymer: hand-to-mouth contact	Toddler or infant crawling on floor	Toddler	2		8.87E-04	8.87E-04
		Infant	2		9.45E-04	9.45E-04
7. Oral exposure to treated polymer: taking into mouth	7.1 Small-scale	Adult	2		3.06E-05	3.06E-05
		Child	2		3.84E-05	3.84E-05
		Toddler	2		9.18E-05	9.18E-05
	7.2 A) Large-scale for infants and toddlers	Toddler	2		6.02E-04	6.02E-04
		Infant	2		2.62E-03	2.62E-03
	7.2 B) Large-scale for children and adults	Adult	2		9.35E-04	9.35E-04
		Child	2		2.35E-03	2.35E-03
8. Oral exposure to treated textile: taking into mouth	Textile taken into mouth by infants or toddlers	Toddler	2		0.062	0.062
		Infant	2		0.027	0.027
9.1 Dermal exposure to treated textile: direct contact with human skin	9.1 Small-scale	Adult	2	0.99		0.99
		Child	2	1.33		1.33
		Toddler	2	1.52		1.52
		Infant	2	1.62		1.62
	9.2 Textile hand contact	Adult	2	0.34		0.34
		Child	2	0.45		0.45
		Toddler	2	0.57		0.57

8.6.8 Combined scenarios

The combination of the scenarios shown above has already been covered by the concept of multiple exposure pattern, i.e. comparing short-term exposure with long-term AEL. This concept is described in chapter 12.6.

8.7 DIETARY EXPOSURE

For applications in PT 4, exposure of the general public is obvious: Humans come into contact with silver migrating into food from treated articles (including surfaces) like, for example, food storage containers, plastic bottles or cutting boards.

Exposure of the general public via food is not expected for applications in PTs 2 and 7. Any kind of treated article used in a way that may enter into contact with food (incl. drinking water) is considered to fall under PT4.

8.7.1 List of scenarios – PT4

Summary table of main representative dietary exposure scenarios			
Scenario number	**Type of use**	**Description of scenario**	Subject of exposure
D1	Food contact materials	Migration from polymers into food (see chapter 8.7.5)	General public
D2	Preservation of water filter	Silver and ions released into drinking water (see chapter 8.7.5)	General public

8.7.2 Information of non-biocidal use of the active substance

Silver-containing active substances, not necessarily silver zeolite, are used in a variety of biocidal and non-biocidal applications.

Summary table of silver substances in other biocidal uses		
Sector of use[1]	**Intended use (examples)**	**Reference value(s) [2]**
Biocides – PT 1	Hand disinfection	For silver ions same as in this CAR
Biocides – PT 2	Disinfection of swimming pools, surface disinfection, laundry detergent	
Biocides – PT 3	Disinfection of animal houses and equipment	
Biocides – PT 4	Surface disinfection	
Biocides – PT 5	Disinfection of drinking water	
Biocides – PT 6	Preservation of paints	
Biocides – PT 7	Preservation of paints	
Biocides – PT 9	Preservation of polymers, odour prevention	
Biocides – PT 10	Mortar, concrete, plaster, grouts	
Biocides – PT 11	Preservative used in recirculating systems	
Biocides – PT 12	circulating waters of cooling systems	

Summary table of silver substances in other <u>non-biocidal</u> uses		
Sector of use	**Intended use**	**Reference value(s)**
Medical devices		PDE[21] (Permitted Daily Exposure): Oralt = 167 µg/d Parenteralt = 14 µg/d Inhalation = 7.0 µg/d
Cosmetic products		
Plant protection products	Active substance: silver thiosulphate Use: Improve quality of flowers after harvest	AOEL = 0.06 µg Ag/kg bw/day[22] The default MRL of 0.01 mg/kg according to Art 18(1)(b) Reg 396 / 2005 applies.
Food additives	Colour E 174	Not established. See text below.
Semiconductor and other electronic articles		Not known
Other	Cutlery, jewellery etc.	Not known

In 2011, EFSA published a scientific opinion on the safety evaluation of the substance silver zeolite A (silver zinc sodium ammonium alumino silicate[23]), silver content 2–5% for use in food contact materials (EFSA, 2011[24]). The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) classified silver zeolite in the SCF list 3 with a specific migration limit of 0.05 mg Ag/kg food based on the human no-observed-adverse-effect level (NOAEL) of about 10 g/kg silver for a total lifetime oral intake (WHO, 2008) for drinking water. However, currently, no silver compounds are approved for use in plastic materials and articles intended to come into contact with food (COMMISSION REGULATION (EU) No 10/2011). We found that it would not be compliant with the ADI. In other words, using the ADI for silver set in this report and default assumptions (amount of food in contact with surface = 1 kg; contact surface area = 6 dm^2) would lead to unacceptable risks for toddlers, children and infants. Note, EFSAs current specific migration limit is derived for adults only.

In 2016, EFSA published is opinion regarding the re-evaluation of the safety of silver (E 174) when used as a food additive[25]. Silver in food additive E 174 is present in its elemental form. The Panel noted that there are data gaps and concerns to be addressed to conduct a risk assessment with respect to the use of silver (E 174): lack of data on toxicity studies on elemental silver or the food additive (E 174); unknown particle size distribution of the food additive (E 174); evidence of the release of silver ions from elemental silver, which may be of concern. However, the extent of the release of the silver ions is unknown

21 ICH GUIDELINE FOR ELEMENTAL IMPURITIES; Q3D; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf
22 EU Pesticides database.
23 This covers silver zinc zeolite, silver zeolite and silver copper zeolite applied for under the BPR
24 Scientific Opinion on the safety evaluation of the substance, silver zeolite A (silver zinc sodium ammonium alumino silicate), silver content 2–5%, for use in food contact materials. EFSA Journal 2011; 9(2):1999. 12 pp.
25 EFSA Journal 2016;14(1):4364 http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4364/epdf

in the case of silver (E 174). The Panel concluded that the information available was insufficient to assess the safety of silver as food additive. The major issues included chemical identification and characterisation of silver E 174 (e.g. quantity of nanoparticles and release of ionic silver) and similar information on the material used in the available toxicity studies. Therefore, the Panel concluded that the relevance of the available toxicological studies to the safety evaluation of silver as a food additive E 174 could not be established. The Panel recommended that the specifications for E 174 should include the mean particle size and particle size distribution (± SD), as well as the percentage (in number) of particles in the nanoscale (with at least one dimension below 100 nm), present in the powder form of silver (E 174) used as a food additive. The methodology applied should comply with the EFSA Guidance document, e.g. scanning electron microscopy (SEM) or transmission electron microscopy (TEM). The Panel recommended that additional data in line with the current Guidance document on evaluation of food additives would be required.

There are no specific MRLs set. However, setting an MRL is likely not warranted because for Food contact materials, which is the case here, specific migrating limits appear to be the preferred option (CA-March17-Doc.7.6.c-final).

8.7.3 Estimating Livestock Exposure to Active Substances used in Biocidal Products

Direct exposure of livestock to the active substance is not expected. Livestock as well as pets and other domestic animals might be exposed indirectly via the consumption of feed that has been in contact with a treated material. In absence of specific guidance for this scenario it is assumed that the risk assessment carried out for consumers also covers the risk for animals.

8.7.4 Estimating transfer of biocidal active substances into foods as a result of professional and/or industrial application(s)

There is no expected dietary exposure that is specific for professionals to the active substances or released silver from the intended uses.

8.7.5 Estimating transfer of biocidal active substances into foods as a result of non-professional use

8.7.5.1 Scenario D1 - Migration from polymers into food

Description of Scenario D1 Migration from polymers into food	
Parameters	**Value [µg * kg^{-1} * day^{-1}]**
Migration from polymers into food simulants. 1 kg of food coming into contact with 6 dm^2 of food contact material consumed per day.	Adult: 2.7-41 Child: 6.8-103 Toddler: 16-247 Infant: 20-309

Details of calculations are found in Appendix II.

8.7.5.2 Scenario D2 – Preservation of water filter

Description of Scenario D2 Migration from treated filters into drinking water	
Parameters	**Value [µg * kg^{-1} * day^{-1}]**
Migration into drinking water. Daily consumption of water for drinking and/or food preparation (EPA exposure factors handbook chapter 3) Adult: 1 L/d Child: 0.48 L/d Toddler: 0.31 L/d Infant: 0.55 L/d	Adult: 0.37 Child: 0.44 Toddler: 0.68 Infant: 1.5

Details of calculations are found in Appendix II.

8.7.5.3 Summary of indirect exposure via food

Details of calculations are found in Appendix II.

Summary table: indirect exposure via food		
Oral absorption: 5%		
Exposure scenario		**Estimated oral uptake**
		µg * kg^{-1} * day^{-1}
Migration from polymers into food simulants	Adult	0.12-2.1
	Child	0.34-5.2
	Toddler	0.81-12
	Infant	1.0-15
Preservation of water filter*	Adult	0.018
	Child	0.022
	Toddler	0.034
	Infant	0.075

* based on study with silver zeolite

8.8 COMBINED RESIDENTIAL SCENARIOS

It is imaginable that humans at home will become exposed while carrying out several activities and simultaneously getting into contact with treated articles or biocidal products releasing silver. The variety of potential combinations of above described scenarios (chapters 8.5 to 8.7) as well as non-biocidal uses is almost infinite. For example, a person manually applying a sealant may – possibly without knowing - use silver-treated plastic articles in their bathroom, use silver treated food packaging and a silver-treated water filter for their table water.
This potential combination of residential scenarios is covered by the concept of multiple exposure described in chapter 12.6.

9 ENVIRONMENTAL EXPOSURE ASSESSMENT

According to the information provided by the applicant, silver zeolite is not incorporated into textiles or articles that are intended to be used outdoors.
General information

Assessed PT	**PT 2**
Assessed scenarios	2.1: Wall and floor covering 2.2: Treated articles – service life (Ventilation and air conditioning components) 2.3: Polymer formulation
Exposure guidance used	2.1: Applicable parts of Supplement to the ESD for PT 2: Emission scenarios for private and public health area disinfectants and other biocidal products (JRC Scientific and Technical Reports, 2011) 2.2: EUSES version 2.1.2 2.3: EUSES version 2.1.2
Approach	2.1: consumption based 2.2: tonnage based 2.3: tonnage based
Distribution in the environment	Vol. 4 Part B (Version 1.0 April 2015) Distribution in STP: measured data
Groundwater simulation	No simulations performed
Confidential Annexes	YES
Life cycle steps assessed	2.1: service life 2.2: service life and waste stage 2.3: use (= incorporation into polymers during formulation)
Remarks	

Assessed PT	**PT 4**
Assessed scenarios	4.1: Polymer formulation 4.2: Treated articles (including water filters) – service life – regional
Exposure guidance used	4.1: EUSES version 2.1.2 4.2: EUSES version 2.1.2, REACH guidance (R.17 "Estimation of Exposure from Articles"), R.18 ("Exposure scenario building and environmental release estimation for the waste life stage"), OECD ESD No. 3, "Emission scenario document on Plastic Additives" (OECD 2009).
Approach	4.1: tonnage based 4.2: tonnage based
Distribution in the environment	Vol. 4 Part B (Version 1.0 April 2015) Distribution in STP: measured data
Groundwater simulation	No simulations performed
Confidential Annexes	YES
Life cycle steps assessed	4.1: use (= incorporation into polymers during formulation) 4.2: service life and waste stage
Remarks	

Assessed PT	**PT 7**

Assessed scenarios	7.1: Polymers used on infrastructure 7.2: Polymer formulation 7.3: Treated articles – service life – regional
Exposure guidance used	7.1: relevant parts of City scenario: Leaching from paints, plasters and fillers applied in urban areas (NL, 2015) 7.2: EUSES version 2.1.2 7.3: EUSES version 2.1.2, REACH guidance (R.17 "Estimation of Exposure from Articles"), R.18 ("Exposure scenario building and environmental release estimation for the waste life stage"), OECD ESD No. 3, "Emission scenario document on Plastic Additives" (OECD 2009).
Approach	7.1: consumption and measured leaching data 7.2: tonnage based 7.3: tonnage based
Distribution in the environment	Vol. 4 Part B (Version 1.0 April 2015) Distribution in STP: measured data
Groundwater simulation	No simulations performed
Confidential Annexes	YES
Life cycle steps assessed	7.1: use and service life 7.2: use (= incorporation into polymers during formulation) 7.3: service life and waste stage
Remarks	The applicant provided information that during 2014 [redacted] tonnes were put on the EU market for PT 7. [redacted]

Biocidal product specific data

The biocidal product AgION® Silver Antimicrobial Type LGK consists to 100% of the active substance.

Type LGK is incorporated into polymers, coatings, laminates, adhesives and sealants at a maximum level of 5.0% by weight (0.25% silver).

Silver zeolite is used in a wide range of treated articles. The substance is incorporated into polymer items and textiles. For treated articles imported into the EU, the active substance evaluation is the only possibility to assess risks connected with these uses. Therefore, all uses suggested by the applicant have been included into the exposure assessment.

An overview over intended uses of silver zeolite is presented in chapter 8. A comprehensive list of uses provided by the applicant during different stages of the evaluation is found in Appendix II. The exposure evaluation focuses on the recently provided information (August 2015 – September 2016)

Migration

The term migration in the dossier is used for the release of silver out of solid carrier material. The migration rate is dependent on different factors like surface area of the type of plastic material, contact time with a solvent, ionic strength of the solvent and on the release of silver from the active substance.
A factor which appears to influence the release of silver considerably is the type of plastic material used. Different plastics have different water absorption characteristics; the greater the tendency of a plastic to absorb moisture, in theory the more silver will be released.

The European Food Safety Authority (EFSA) concluded that the plastic material has a decisive influence: Out of different plastic materials treated with AgION Silver Zeolite, only some are suitable for food contact material. EFSA's Scientific Panel on food additives (EFSA 2005) voted that AgION can only be used in polyolefins (up to 40°C) for contact times below 1 day, and in poly(alkylene terephthalate) base polymers (up to 99°C) for contact times below 2 hours. In PVC and polystyrene based polymers, the migration far exceeded 50 µg/kg food (simulating solvent); for these materials, use of silver zeolite was not recommended to be authorized for food contact materials. In so far, the EFSA statements are congruent with the migration tests submitted in the context of this application.

Migration data submitted for silver zinc zeolite show that silver was migrating from PVC more than double as fast as from LDPE. In the order from lowest two highest migration the polymers tested were: PBT<LDPE<polystyrene<PVC (Sciessent III B 6.7.1.2-01 – 06). Polyamide has a higher water absorption rate than many other polymers, and migration will theoretically be even higher from this polymer type. However, polyamide was not among the polymers tested. On the other hand, migration studies recently submitted by another member of the European Silver Task Force showed that the influence of polymer type is less pronounced that previously assumed. Migration rates vary within a factor of approximately 5 among tested polymer types, including polyamide, for the silver compound tested.

Although outdoor use of treated articles and textiles is not intended, silver might be released when articles are washed or cleaned, or when floors are cleaned, etc. The applicant as not provided migration test carried out under conditions that are relevant for the intended use. We propose to use migration data submitted by the applicant for silver zinc

zeolites, because the release data with pure zeolites show that release rates are comparable.

Comparison of release rates with silver zeolite (SZ) and silver zinc zeolite (SZZ) (see chapter 1.3.1 of respective CAR)

Interval (Hours)	Distilled water, 20°C				Phosphate buffer, pH 4, 37°C				Phosphate buffer, pH 8, 37°C			
	SZ		SZZ		SZ		SZZ		SZ		SZZ	
	Ag release (%)	pH	Ag release (%)	pH	Ag release (%)	pH	Ag release (%)	pH	Ag release (%)	pH	Ag release (%)	pH
3	<0.02	6.6	0.07	9.3	16.3	4.5	42.2	4.5	12.7	7.9	18.1	8.1
6	n.a.	2.9	0.09	9.1	23.2	4.7	39.7	4.5	14.4	7.9	16.0	8.0
12	<0.02	8.6	0.10	9.1	28.0	4.8	38.1	4.5	14.0	7.9	13.7	8.1
18	<0.02	8.3	0.11	8.9	31.1	4.7	37.4	4.4	13.7	7.9	12.5	8.1
24	<0.02	8.4	0.11	8.7	33.3	4.8	36.7	4.4	14.0	7.9	12.2	8.1
72	<0.02	8.6	0.13	8.8	38.7	4.8	37.0	4.6	14.2	7.9	13.2	8.1
168	<0.02	8.8	0.15	8.8	40.7	4.9	40.4	4.6	15.4	7.9	13.8	8.0

Migration has been estimated in a laboratory experiment involving immersion of polypropylene coupons containing silver zinc zeolite in deionised water over 30 days at 25°C (IIIB 6.6-01 BASF (Ciba) in dossier for silver zinc zeolite). Initially and after 30 days up to 0.002% of the nominal silver contained in the polymer had migrated out. At intermediate time points the silver concentration in the medium decreased, which makes the results more uncertain since no trend could be observed. The disappearance of silver could possibly be explained by adsorption to test vessels or precipitation. Considering that the samples were filtered before analysis, precipitated silver might have been omitted. Additionally, or alternatively, dissolved silver may have been adsorbed to the filter material (in the positive controls recovery was 80-120%, but concentrations were generally much higher, so the recovery might not be representative for the lower concentrations in the test). A long-term leaching rate cannot be determined based on these results. However, when taking into account the results with polyester fabric, it appears reasonable to assume that the major part of silver will have been migrated out already during the first 30 days. Therefore, we apply the initial migration rate for the first 30 days (time1), after that we assume the migration has dropped to 10% of the initial migration rate. In this case, considering solid polymer, the amount leached from the polymer related to surface of the test item can be used, multiplied by correction factors as follows:

The applicant has not provided information about release under realistic outdoor conditions.
Deionised water is not the worst case medium for ion-exchangers like zeolites. Migration speed also depends on the composition of the medium. It is a property of ion-exchangers like zeolites that silver and zinc ions are released from the zeolite in the presence of substitute ions in the medium. The release study with pure silver zinc zeolites (chapter 1.3.1) clearly illustrates that migration is much slower in deionised water than in hard water. In hard water, up to 2.3 % of silver was released from the zeolite after 168h. Release in hard water is 2 to 15 times higher than in deionised water under the same conditions. Thus, for the purpose of this risk assessment, the migration speed determined in the 30-day release study is multiplied **by a factor of 10**. The active substance concentration in the test item was 1.5% containing 3.6% silver. To cover the applications containing up to 5% active substance, a **correction factor of 3.33** was applied.
Migration depends on the water absorption rate of the polymer type, which has been discussed in chapter 9.2.1. This means that the experimentally derived release data are

strictly only valid for the tested polypropylene, not for other polymers. Migration depends on the polymer type. Migration varies by a factor of around 5 among different tested polymers treated with silver zinc zeolite. Migration from polypropylene is in the middle to upper range. Therefore, we apply a **correction factor of 2** to correct for the variability among polymers. To summarise, the leached amount after 30 days in the laboratory test is multiplied by a factor of 66.67.

Reliable data for the release of zinc from treated polymers are not available. Therefore, the same migration rate as for silver is assumed, extrapolated to the zinc content in the product/active substance.

Migration of silver from polypropylene into distilled water

Reference	Product type	Polymer type	Conc. of product in polymer	Conc. of silver in product	Conc. of silver in polymer	Duration	Test medium	Correction factor	Migration rate
			%	%	%	d			µg * cm^{-2} * d^{-1}
IIIB 6.6-01 BASF (Ciba) in dossier for silver zinc zeolite	Irgaguard B 8000	PP	1.5	3.6	0.054	30	Distilled water	66.67	0.0019

9.1 EMISSION ESTIMATION

9.1.1 Scenario 2.1 – Wall and floor covering

Wall or floor covering for use in locations where a hygienic environment is desirable, are uses mentioned by the applicant in the dossier provided in July 2015. The product is incorporated into the polymer matrix of the wall or floor covering. The standard emissions scenarios for PT2 are not applicable, since there is no given amount of cleaning product used. Instead, silver will become released from treated floor when wet-cleaned. Walls might occasionally be wet-cleaned, but are not expected to contribute significantly to release of silver to the environment.

Consumption based scenario:
We use the default surface area cleaned in industrial and institutional areas (1000 m^2, ESD PT2) in order to estimate the release of silver during cleaning. We assume that silver is released at the rate determined in the migration test with distilled water (details in introduction to chapter 9). We further assume that the room is cleaned once per day every day, and that the cleaning water has contact with the flooring for a duration of 30 minutes.

For further details, see Appendix III.

9.1.2 Scenario 2.2 – Treated articles – service life (Air-conditioning components)

Air conditioning components, mattresses and medical furniture are among the uses mentioned by the applicant in the information provided in August 2015. The biocidal product (= active substance) is incorporated into the polymer matrix of the components. The applicant claims a maximum silver content in the polymer of 0.25%.

Consumption based scenario:
For air-conditioning components, in order to assess the exposure to water, more information would be needed. Either the area of the component in contact with water in relation to the amount of water passing through, or the effective concentration in the water would be necessary to know. Such information was not made available by the applicant. Therefore, the standard emission scenarios for PT2 are not applicable and consumption based exposure assessment for air conditioning systems cannot be carried out.

Tonnage based scenario:
Since both for air conditioners and for PT 4 uses, the exposure category "wet " applies, the exposure is exactly the same for air conditioners as for PT4. All further details of the scenario used are found in the emission estimation for PT 9.2.

9.1.3 Scenario 2.3 - Polymer formulation

Tonnage based scenario:
For the release during polymer production. EUSES version 2.1.2 was used for the simulations.
The assumptions about the formulation steps are exactly the same for PT 2, 4 and 7. All further details of the calculations are found in the emission estimation for PT 4 (scenario 4.1).

9.1.4 Scenario 4.1 - Polymer formulation

Tonnage based scenario:
For the release during polymer production. EUSES version 2.1.2 was used for the simulations.
For the release during polymer production. EUSES version 2.1.2 was used for the simulations.
The assessments were conducted for the life-cycle phase industrial use. The calculations were based on the tonnage of silver going into polymer consumer articles. The physical and chemical model input parameters are based on silver.

For further details, see Appendix III.

9.1.5 Scenario 4.2 - Treated articles – service life – regional

Polymer kitchen utensils, water filters, food packaging, food containers, tubing, food processing equipment are uses mentioned by the applicant in the information provided August 2015 – September 2016.

Tonnage based scenario:
Since no further information is available about distribution of the tonnage among exposure categories, the exposure category "wet " applies to the whole tonnage. This includes also

the use in water filters. All further details of the calculations are the same as for PT 9 and found in the emission estimation for scenario 9.2.

For further details, see Appendix III.

9.1.6 Scenario 7.1 - Polymers used on infrastructure

We define infrastructure as coatings on buildings or immobile constructions, i.e. those uses that are described in the ESD for PT8 and in the City Scenario.

Consumption based scenario:
Coatings and paints and sealants are among uses mentioned by the applicant, but only indoor uses are intended. Release to the sewage is expected from use of sealants in bathrooms. To cover this, exposure from these uses will be assessed with help of the relevant scenario in the City scenario: Leaching from paints, plasters and fillers applied in urban areas (NL, 2015).

For further details, see Appendix III.

9.1.7 Scenario 7.2 - Polymer formulation

Tonnage based scenario:
For the release during polymer production. EUSES version 2.1.2 was used for the simulations.
The assumptions about the formulation steps are exactly the same for PT 2, 4 and PT 7. Therefore, all further details are found in the emission estimation for PT 4 (scenario 4.1).

9.1.8 Scenario 7.3 - Treated articles – service life – regional

Tonnage based scenario:
The concept described in scenario 9.4 is here used for exposure assessment of migration for silver from treated polymer articles for PT7 as well. Since no further information is available about distribution of the tonnage among exposure categories, the exposure category "wet " applies to the whole tonnage. All further details are the same as for PT 9 and found in the emission estimation for scenario 9.2.

For further details, see scenario 9.4 and Appendix III.

9.1.9 Scenario 9.2 - Polymer formulation

Tonnage based scenario:
For the release during polymer production. EUSES version 2.1.2 was used for the simulations.
The assumptions about the formulation steps are exactly the same for PT 2, 4 and PT 7. Therefore, all further details are found in the emission estimation for PT 4 (scenario 4.1).

9.1.10 Scenario 9.4 - Treated articles (including textiles) – service life – regional

Note: The general concept of exposure assessment has been agreed upon at the TM IV 2013 when the CAR for silver zinc zeolite was discussed. The agreed concept regards the exposure categories. release default values. distribution in the environment and the EUSES input parameters. The Working group asked the eCA to conduct separate exposure assessments for silver-containing substances and product type. However. the working group also recognized that combined exposure assessment has to be done. The combined exposure assessment for silver-containing active substances is presented in a separate document

Tonnage based scenario:
Silver zeolite is one of a number of silver-containing active substances that are used to provide antimicrobial properties or functions to treated articles. Environmental exposure from treated articles is diffuse due to the variety of articles which can be treated with silver (and other ions where it applies). and due to the diversity of uses. This variety of uses causes a great variety of exposure situations. However. to be able to make a realistic exposure assessment. it was necessary to summarize and to simplify exposure situations. Therefore. we generally used the tonnage approach for all exposure situations which are diffuse. This approach is supported by REACH guidance (R.17 "Estimation of Exposure from Articles"). It says:
"To calculate exposure for the environment. the estimated loading of the environment is calculated from release rates and the tonnage of the substance contained in the articles.

Subsequently. the calculated or measured overall emission is treated as any other environmental emission in the current exposure estimation. The emissions during service life are considered to be diffuse emissions that usually cause exposure on a "regional" scale. …" For this exposure assessment. the life cycle stages polymer production. service life and waste are taken into account. We do not distinguish between consumer use (usually used for liquid consumer products) and service life (usually used for articles) as this is not a meaningful category for this exposure assessment. We define both belonging to the life cycle stage service life.

Note, that the exposure estimates are made based on the tonnage data provided by the applicant for the amount of biocidal product/substance placed on the EU market. This includes the product used in treated articles imported into the EU.

Note, that the exposure estimates are made based on the tonnage data provided by the applicant for the amount of biocidal product/substance placed on the EU market. This includes the product used in treated articles imported into the EU.

For further details, see Appendix III.

9.2 FATE AND DISTRIBUTION IN EXPOSED ENVIRONMENTAL COMPARTMENTS

Identification of relevant receiving compartments based on the exposure pathway									
Scenario	**Fresh-water**	**Sediment**	**Sea-water**	**Seawater sediment**	**STP**	**Air**	**Soil**	**Ground-water**	**Other**
2.1 – Wall and floor covering	YES	YES	(YES)*	(YES)*	YES	Negligible	YES	YES	-
2.2 – Treated articles – service life	YES	YES	(YES)*	(YES)*	YES	Negligible	YES	YES	-
2.3; 4.1; 7.2– Polymer formulation	YES	YES	(YES)*	(YES)*	YES	Negligible	YES	YES	-
4.2; 7.3– Treated articles/textiles – service life	YES	YES	(YES)*	(YES)*	YES	Negligible	YES	YES	-
4.3; 7.3; – Treated articles – combined exposure	YES	YES	(YES)*	(YES)*	YES	Negligible	YES	YES	-
* the risk assessment for freshwater covers even the risk for the marine freshwater and sediment									

Input parameters (only set values) calculating the fate and distribution of silver in the environment			
Input	Value	Unit	Remarks
Molecular weight	107.87	g/mol	
Melting point	500	°C	The melting point of silver is in the order of 1000°C, however the value was set to 500°C as the maximum value recommended within the EUSES model.
Boiling point	500	°C	The boiling point of silver is in the order of 2000°C, however the value was set to 500°C as the maximum value recommended within the EUSES model.
Vapour pressure (at X °C)	1×10^{-6}	Pa	Silver has negligible volatility and the value was set to 1×10^{-6} Pa as the minimum recommended within the EUSES model.
Water solubility (at X °C)	$1 * 10^{-3}$	mg/l	Silver has very low water solubility and the value was set to $1 * 10^{-3}$ mg/L as the minimum recommended within the EUSES model.
Log_{10} Octanol/water partition coefficient	-	---	Not applicable for inorganic metal compound
Kp_{soil}	398.11	cm^3/g	
Kp_{susp}	1×10^5	cm^3/g	Measured Kp_{susp}= 1.585×10^5 cm^3/g. 1×10^5 is the maximum recommended by the EUSES model.
Degradability			Not applicable for inorganic metal compound

Calculated distribution of silver in the STP		
Compartment	Percentage [%]	Remarks

Air	0	Not volatile
Water	9	Measured data
Sludge	91	
Degraded in STP	0	Not degradable

9.3 CALCULATED PEC VALUES

Summary table on calculated PEC values					
Scenario	PEC_{STP} [mg/L]	PEC_{water} [mg/L]	PEC_{sed} [mg/kg_{wwt}]	PEC_{soil} [mg/kg_{wwt}]	PEC_{GW} [mg/L]
2.1 – Floor covering	1.78E-08	7.13E-10	0.000	6.58E-06	1.87E-08
2.2 – Treated articles – service life	3.60E-08	1.70E-09	3.70E-05	1.34E-05	3.80E-08
2.3 – Polymer formulation	4.28E-06	1.71E-07	3.72E-03	1.58E-03	4.49E-06
4.1 – Polymer formulation	4.28E-06	1.71E-07	3.72E-03	1.58E-03	4.49E-06
4.2 – Treated articles – service life	3.60E-08	1.70E-09	3.70E-05	1.34E-05	3.80E-08
7.1 – Polymers used on infrastructure					
City scenario					
Sealants indoor, application, amateur	3.45E-06	1.38E-07	3.00E-03	1.27E-03	3.63E-06
Sealants indoor, application, professional	2.07E-06	8.28E-08	1.80E-03	7.64E-04	2.18E-06
Sealants indoor, service-life, 100% leaching	7.56E-05	3.03E-06	6.57E-02	2.79E-02	7.95E-05
Sealants indoor, service-life, leaching rate	9.86E-08	3.94E-09	8.56E-05	3.64E-05	1.04E-07
7.2 – Polymer formulation	4.28E-06	1.71E-07	3.72E-03	1.58E-03	4.49E-06
7.3 – Treated articles – service life	3.60E-08	1.70E-09	3.70E-05	1.34E-05	3.80E-08
Aggregated exosure	*See chapter 13.7*				

9.4 PRIMARY AND SECONDARY POISONING

Primary poisoning is not expected due to the described use patterns of silver compounds. A semi-quantitate risk assessment of secondary poisoning via the sediment food chain, using available bird and mammalian studies, shows that secondary poisoning is not likely. See chapter 13.6.

10 ASSESSMENT OF EFFECTS ON HUMAN HEALTH FOR THE PRODUCT

10.1 PRODUCT(S)

The representative formulation consists of 100% active substance.

10.2 DERMAL ABSORPTION

Please refer to the dermal absorption data presented in part A. There is no study available in which the dermal absorption of silver zeolite has been tested. Based on the information in part A, section 3.1, 5% of silver ions released from silver zeolite is assumed to be absorbed through the skin.

Value(s) used in the Risk Assessment – Dermal absorption	
Value(s)*	5%
Justification for the selected value(s)	See part A, section 3.1.

* please include the concentration range(s) the values are applicable for, if relevant

Data waiving	
Information requirement	Dermal absorption data for the representative formulation is not available.
Justification	Since the representative formulation consists of 100% active substance, the conclusions made in part A, section 3.1 are valid also for this section.

10.3 ACUTE TOXICITY

Please refer to the acute toxicity data presented in part A.

10.3.1 Overall conclusion on acute toxicity

Value used in the Risk Assessment – Acute toxicity	
Value(s)	The LD50 and LC 50 values set for acute systemic effects via oral, dermal or inhalation routes are above the upper limits for classification.
Justification for the selected value	The conclusion is based on results from animal data with AgION Antimicrobial Type AD.
Classification for the product according to CLP and DSD	AgION Antimicrobial Type LGK is not expected to meet criteria for classification.

10.4 CORROSION AND IRRITATION

Please refer to the dermal absorption data presented in part A.

Overall conclusion on corrosion and irritation

Conclusion used in the Risk Assessment – Corrosion and irritation	
Value(s) or Conclusion(s)	AgION Antimicrobial Type AD is irritating to eyes but the mean scores do not fulfil criteria for classification. Consequently AgION Antimicrobial Type LGK is not expected to meet criteria for classification.
Justification for the selected value/ conclusion	The conclusion is based on results from animal data obtained with AgION Antimicrobial Type AD.
Classification of the product according to CLP and DSD	AgION Antimicrobial Type LGK is not expected to meet criteria for classification.

10.5 SENSITISATION

Please refer to data presented in part A.

10.5.1 Skin sensitisation

Conclusion used in Risk Assessment – Skin sensitisation	
Value/conclusion	The data available do not indicate a skin sensitising potential of AgION Antimicrobial Type LGK.
Justification for the value/conclusion	The conclusion is based on results from a LLNA test in mice.
Classification of the product according to CLP and DSD	AgION Antimicrobial Type LGK does not fulfil criteria for classification as a skin sensitiser.

10.5.2 Respiratory sensitisation

No data available.

10.5.3 Overall conclusion on sensitisation

Conclusion used in the Risk Assessment – Sensitisation	
Conclusion(s)	Data do not indicate a skin sensitising potential of AgION Antimicrobial Type LGK.
Justification for the conclusion(s)	The conclusion is based on results from a LLNA test in mice.
Classification of the product according to CLP and DSD	AgION Antimicrobial Type LGK does not fulfil criteria for classification as a skin sensitiser.

10.6 OTHER

There are two additional studies available investigating silver migration from silver zeolite impregnated urethane (TPU) from LDPE and pillow cases after exposure into simulated human sweat and saliva media. This information is considered in the expsosure assessments in part B.

11 ENVIRONMENTAL EFFECTS ASSESSMENT FOR THE PRODUCT

The representative formulation consists of 100% active substance.

Part C Risk characterisation of the biocidal product(s)

12 RISK CHARACTERISATION FOR HUMAN HEALTH

12.1.1 Systemic effects

Preferably, the acceptable exposure level (AEL) should be derived based on a NOAEL set in a reliable study performed during a time period which is relevant for the intended use scenario.
According to the applicant, silver zeolite is incorporated into polymers which are then used to form a range of end-use items with uses in product types 2, 4 and 7.
This means that professional users incorporating AgION Antimicrobial Type LGK into coatings will be exposed to the active substance whereas consumers will be exposed to silver ions (and possibly other constituents of the active substance) released from treated articles. Consequently, AELs are needed both for the active substance and for silver ion equivalents.
Exposure of professional/industrial users is expected to be of long-term duration. Due to the broad range of consumer articles treated with the active substance or other SCAS relasing silver ions, the exposure of non-professional users/consumers is considered to be of chronic duration (due to sequential or simultaneous exposure) despite that each separate scenario could be considered to acute or medium-term exposure. The NOAELs set in studies relevant for the derivation of a short-term, medium-term and long-term AEL for the active substance and the silver ion, respectively, are shown in the table below.

Duration	Study	Route	Relevant effects	NOAEL/ LOAEL	References
Acute	Silver copper zeolite Developmental toxicity study Reliability: 1-2	Oral	No acute effects noted. (reduced body weight starting from GD 10)		Doc IIIA 6.8.1(02)
28 day	Copper sulfate 28 day study	Oral	28 day study Damage to the liver, kidney, and the hematopoietic system	377 mg/kg bw/d*	Assessment report for Copper sulfate pentahydrate Product-type 2, September 2013
28 day study	JMAC 4 week gavage study in rat	Oral	Discoloration along capillary basement membranes Brown/black particulate material in the lamina propria macrophages discoloration of lymph node sinusoids.	571 mg/kg bw/d**	IIIA 6.3.1(02)
Medium-term	Silver sodium hydrogen zirconium phosphate 13 week rat study Reliability: 1	Oral	Pigmentation of the pancreas and harderian gland in females Increased ALP in males	21 mg/kg bw/d***	IIIA 6.4.1 (04) (1995)
Long-term	Silver zinc zeolite Type AJ Combined chronic and carcinogenicity 105 week rat study (non GLP) Reliability: 2-3	Oral	Pigmentation of liver, kidneys, pancreas, stomach, lymph nodes and the choroid plexus	6 mg/kg bw/d****	IIIA 6.5 (06) (1992b)

* Estimated from data on copper sulfate based on copper content and 100% release of copper in silver copper zeolite.

** Estimated from data on the reaction mass of titanium dioxide and silver chloride

***Estimated from a back-calculation of the NOAEL set for silver sodium hydrogen zirconium phosphate based on the silver content and expected silver release of silver copper zeolite (see part A, section 1.3.1).

****Estimated from a back-calculation of the NOAEL set for silver zinc zeolite based on the silver content and expected silver release of silver copper zeolite (see part A, section 1.3.1).

Silver ion equivalents

Duration	Study	Route	Relevant effects	NOAEL/ LOAEL	References
Acute	No acute effects noted				
Medium-term	13 week rat study	Oral	Increased level of ALP (males), pigmentation of the Harderian gland(females)	0.3 mg/kg bw/d	IIIA 6.4.1 (04) (1995)
Long-term	105 week combined chronic and carcinogenicity study in rat (F344) Silver zinc zeolite ,AgION Zeomic AJ 10N 0.01, 0.03, 0.1 and 0.3%,"at least" 0, 3, 9, 30 and 87 mg /kg bw/day)	Oral	Pigmentation of liver, kidneys, pancreas, stomach, lymph nodes and the choroid plexus	0.09 mg Ag^+ eq/ kg bw/d	IIIA 6.5 (06) (1992b)

As seen in the table below, pigmentation of organs and tissues is an effect considered for the LOAELs in all studies conducted (data from Doc IIIA of the core dossier). The pigmentation observed is assumed to be due to the deposition of silver and is an effect specific to the silver in the SCAS.
Deposition of silver particles in tissues and organs is an undesired effect and it cannot be excluded that accumulation over time may result in adverse effects. The AEL set must thus ensure that exposure to SCAS does not exceed the ability of the body to excrete silver.
The NOAELs in the table below are estimates based on results from studies in which the silver ion has been indirectly tested. They do not represent true NOAEL and this may, to some extent, explain discrepancies between results. The lowest NOAELs for medium-term and long-term toxicity of the silver ions are set in the 90-day rat study with silver sodium hydrogen zirconium phosphate and the 105 week combined chronic and carcinogenicity rat study, respectively. Based on these NOAELs, an oral absorption of 5% and a safety factor of 100, medium-term and long-term AELs of 0.15 µg/kg bw/d and 0.045 µg/kg bw/d can be derived and used for the risk assessment of silver ion equivalents. In case a short-term AEL would be needed, this would be derived on the same basis as the medium-term AEL.

NOAELs set in repeated dose toxicity studies. Studies in which pigmentation was observed at the LOAEL is shown in bold style.

SCAS	NOAEL (mg SCAS/kg bw/d)	NOAEL (mg Ag+//kg bw/d)	LOAEL (mg SCAS/kg bw/d)	LOAEL (mg Ag+/kg bw/d)
Short-term studies				
silver chloride adsorbed onto titanium dioxide	**250***	**~2.7***	**500***	**~5.3***
* Short–term NOAEL extrapolated from sub-acute NOAEL by the use of an uncertainty factor of 3				

silver sodium hydrogen zirconium phosphate (rat)	**30**	**~0.3**	**300**	**~3**
silver sodium hydrogen zirconium phosphate (dog)	**400**	**~5**	**200**	**~10**
silver zinc zeolite (rat)	**64/78**	**~1.3**	**398/489**	**~8.2**
silver zinc zeolite (dog)	**50**	**~1.0**	**250**	**~5.1**
Reproduction studies				
Silver copper zeolite (teratogenicity study, rat)	700 (maternal) >2000 (pups)	~10 (maternal) >29 (pups)	2000 (maternal) >2000 (pups)	~29 (maternal) >29 (pups)
silver sodium hydrogen zirconium phosphate (teratogenicity study, rat)	>1000 (maternal, pups)	>25 (maternal, pups)	>1000 (maternal, pups)	>25 (maternal, pups)
silver sodium hydrogen zirconium phosphate (2-generation study, rat)	**72/78 (parents, pups) 400 (reproduction)**	**~1.9 (parents, pups) ~9.9 (reproduction)**	**363/400 (parents, pups) 1612 (reproduction)**	**~9.9 (parents, pups) ~40 (reproduction)**
silver zinc zeolite (2-generation study, rat)	**NA (parents, pups) 70**	**NA (parents, pups) 1.4 (reproduction)**	**m/f ≤72/87 (parents, pups) 443 (reproduction)**	**m/f ≤1.5/1.8 (parents, pups) 9 (reproduction)**
Long-term effects				
silver zinc zeolite (mouse)	**NA**	**NA**	**≤67**	**≤~0.67**
silver zinc zeolite (rat)	**9**	**~0.09**	**30**	**~0.29**

12.1.2 Local effects

Route	Effect	Study	Classification	Hazard category[1]
Dermal	There are no indications of local toxicity in the acute dermal toxicity study or in the sub-chronic dermal toxicity study. Initial and transient skin and eye reactions were noted in the irritation studies but effects do not fulfil criteria for eye irritation.		Effects do not meet criteria for irritation.	Not relevant
Respiratory	No indications in the acute inhalation toxicity study.		Not relevant	

[1] *According to the guidance "Risk characterisation for local effects including sensitisation" – reference to be updated when the guidance is integrated into ECHA guidance.*

12.1.3 Absorption

Route	Study	Test substance	Concentration of test substance	Applicability (concentration ranges)	Value
Oral	Furchner et al. 1968 *in addendum to Doc. IIIA, section 6*	Silver nitrate	Unknown	all	5% (see chapter 3.1.2)
Dermal	No data available				5% (see chapter 3.1.2)
Inhalation					100% (see chapter 3.1.2)

12.2 REFERENCE VALUES

12.2.1 Uncertainties and assessment factors

There is no short-term toxicity data on silver zeolite. The short-term toxicity studies performed with silver sodium hydrogen zirconium phosphate did not indicate any acute effects. Therefore, in case a short-term AEL is needed for risk assessment of certain scenarios, the medium-term AELs derived for the active substance and for silver ion equivalents respectively can be used.

$AEL_{medium-term}$		
Uncertainty	**AF**	**Justification**
Interspecies variability	10	
Intraspecies variability	10	
Route to route extrapolation	-	Similar effects were observed in acute toxicity studies following a single high dose via oral and dermal administration and via inhalation
Time duration extrapolation	-	The value is derived from a study of short-term duration (90 days)
NOAEL to LOAEL extrapolation	-	
Dose response	-	
Severity of key health effects	-	Deposition of silver in organs and tissues is considered to be an undesirable effect but the consequences for human health is not clear.
Overall AF	**100**	(n.a.)

$AEL_{long-term}$		
Uncertainty	**AF**	**Justification**
Interspecies variability	10	
Intraspecies variability	10	
Route to route extrapolation	-	Similar effects were observed in acute toxicity studies following a single high dose via oral and dermal administration and via inhalation
Time duration extrapolation	-	The value is derived from a study of long-term duration (104 weeks)
NOAEL to LOAEL extrapolation	-	
Dose response	-	
Severity of key health effects	-	Deposition of silver in organs and tissues is considered to be an undesirable effect but the consequences for human health is not clear.
Overall AF	**100**	(n.a.)

12.2.2 Reference values to be used in Risk Characterisation

Reference	Study	NOAEL (LOAEL)	AF	Correction for oral absorption	Value
$AEL_{short-term}$	If needed for risk assessment, the short-term AEL is proposed to be the same as the medium-term AEL.				
$AEL_{medium-term}$	6.4.1 (04) (1995) Oral 13 weeks Rat (Crl:CDBR VAF Plu) Novaron AG-300 (AlphaSan RC5000) 0, 30, 300 and 1000 mg/kg bw/day	21 mg/kg bw/d*	100	0.05	0.01 mg/kg bw/d
$AEL_{long-term}$	6.5 (06) (1992b) 105 week Combined chronic and carcinogenicity study in rat (F344) Silver zinc zeolite Type AJ,AgION Zeomic AJ 10N 0.01, 0.03, 0.1 and 0.3%,"at least" 0, 3, 9, 30 and 87 mg /kg bw/day)	6 mg/kg bw/d**	100	0.05	0.003 mg/kg bw/d
ARfD	Not relevant, see text below.				
ADI	6.5 (06) (1992b)	6/mg/kg bw/d**	100	-	0.06 mg/kg bw/d
Reference values for silver ion equivalents					
AEL short-term	If needed for risk assessment, the short-term AEL is proposed to be the same as the medium-term AEL.				
AEL medium-term	6.4.1 (04) (1995) Oral 13 weeks Rat (Crl:CDBR VAF Plu) Novaron AG-300 (AlphaSan RC5000) 0, 30, 300 and 1000 mg/kg bw/day	0.3 mg/kg bw/d**	100	0.05	0.15 µg/kg bw/d
AEL long-term	6.5 (06) (1992b) 105 week Combined chronic and carcinogenicity study in rat (F344) Silver zinc zeolite Type AJ,AgION Zeomic AJ 10N 0.01, 0.03, 0.1 and 0.3%,"at least" 0, 3, 9, 30 and 87 mg /kg bw/day)	0.09 (0.3) mg/kg bw/d**	100	0.05	0.045 µg/kg bw/d

ARfD	Not relevant (no acute effects anticipated following single exposure), see text below.				
ADI	6.5 (06) (1992b)	0.09 mg/kg bw/d	100	-	0.9 µg/kg bw/d
*Estimated based on the NOAEL set for silver sodium hydrogen zirconium phosphate. **Estimated based on the NOAEL set for silver zinc zeolite.					

Acute reference dose (ARfD): The ARfD represents the maximum dose of a substance that can be ingested on a single occasion without bringing an unacceptable risk to human health. The ARfD is usually derived from a NOAEL set for an acute effect observed after a single administration via the oral route. According to the guidance document developed within the plant protection process, the NOAEL set for the most sensitive species is commonly used as the basis for the ARfD.
Since effects are observed only following repeated exposure to the SCAS tested, there is no need for an ARfD, neither for the active substance nor for the silver ion equivalents.

Acceptable daily intake (ADI): The ADI represents the maximum dose of a substance that can be ingested on a daily basis without bringing an unacceptable risk to human health. The ADI is usually derived from a NOAEL set in a long-term study performed via the oral route.
Since silver zeolite will be added to a masterbatch and subsequently incorporated into a range of consumer articles, the active substance is expected to remain in the article whereas silver ions will be released from the article and may end up in food. Therefore, only an ADI for silver ion equivalents is needed.
The only study available in the core dossier in which the long-term effects of silver ions have been (indirectly) tested is the chronic toxicity/carcinogenicity study performed with silver zinc zeolite Type AJ. Assuming that all effects observed (i.e. pigmentation of organs and tissues) can be ascribed the silver ion, a long-term NOAEL of 90 µg/kg bw/d can be estimated for silver ion equivalents (based on the silver content and release at conditions assumed to resemble the gastrointestinal tract (pH 4, 37ºC, phosphate buffer)).

Comment:
Reference values for silver has been derived by the US EPA: a toxicity assessment of silver was performed in 1980 in order to recommend an ambient water quality criteria. Although an overall NOEL of 0,008 mg/L[26] was proposed in the document, the US EPA concluded that the animal toxicity data considered in the report did not present compelling evidence to change the standard drinking water limit of 50 µg/L accepted by the National Academy of Sciences (1977). This standard has been set to protect from argyria and is calculated as the maximum daily intake possible during an exposure period of 55 years without exceeding 1g of accumulated silver[27].
Another risk assessment made by the US EPA was presented in 1996 (Integrated Risk Information System). This risk assessment is mainly based on case reports and published data (presented in IIIA, section 6.2(03)). The general oral reference dose for silver is set at 0.005 mg/ kg bw/day based on the lowest dose reported to result in argyria in humans. This reference dose is derived from the conversion of an intravenous dose of 4 g silver asphenamine (corresponding to 1 g metallic silver) into an oral dose of 25g. This value is

[26] Based on a NOEL of 0.8 mg/L in a 70 kg adult and a safety factor of 100
[27] Based on a daily water consumption of 2L and 50% retention of silver in the body.

further adjusted for the bodyweight of an adult (70 kg), 25500 days of exposure (representing 70 years) and an uncertainty factor of 3.
However, in later US EPA risk assessments of silver substances, this oral reference dose has been changed to 0.001 mg/kg bw since it was considered more appropriate to use an uncertainty factor of 10.
Converting this oral reference dose into a systemic dose by adjusting for an oral absorption of 5%, a systemic reference value of 0.05 µg/kg bw/day is obtained. This is comparable to the systemic AEL 0.045 µg/kg bw/day derived for silver ion equivalents in this report.
Moreover, a systemic AOEL of 0.06 mg/kg bw/day has been set for sodium silver thiosulfate during the review of active substances in plant protection products under Regulation No 1107/2009. Based on a silver content of 1%, an AOEL for silver was set at 0.00006 mg/kg bw/d (0.06 µg/kg bw/day). This reference value is also based on pigmentation and is comparable to the AOEL proposed for silver ion equivalents in this review.
The background document for the development of WHO Guidelines for Drinking-water Quality (2003) states that a total lifetime oral intake of about 10 g of silver (equal to 0.39 mg/day/person) can be considered as the human NOAEL. This value is also based on the publication from 1935 by Gaul LE and Staud AH. However, in the updated WHO Guidelines for Drinking-water Quality from 2011 it is stated that "available data inadequate to permit derivation of health-based guideline value".
The NOAELs set by EPA and WHO are based on human case reports describing visible pigmentation of skin (external) in a syphilic patient treated with silver arsphenamine. The ADI set in the dossier is also based on pigmentation but is derived from more recent animal studies in which pigmentation of organs and tissues (internal) is observed at lower doses. This information was not available to the WHO and is considered more robust than the case reports from 1935. Especially taking into account that the human data is based on visible pigmentation of skin and the dose at which (internal) pigmentation of organs and tissues occurs in humans is not known.

12.2.3 Maximum residue limits or equivalent

The default MRL of 0.01 mg/kg according to Art 18(1)(b) Reg 396 / 2005 applies. The present risk assessment indicates that this default MRL might be exceeded in food that comes in contact with a treated surface.
The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) classified silver zeolite in the SCF list 3 with a specific migration limit of 0.05 mg Ag/kg food.

12.2.4 Specific reference value for groundwater

Not available

12.3 INDUSTRIAL USES

12.3.1 Systemic effects

12.3.2

Task/ Scenario	**Tier**	**Systemic NOAEL** mg/(kg bw x d)	**$AEL_{long-term}$** mg/(kg bw x d)	**Estimated uptake** mg/(kg bw x d)	**Estimated uptake/ AEL** (%)	**Acceptable** (yes/no)
	Tier 1	6	0.003	0.018[#]	603	No

Scenario 1 mixing and loading				0.015¤	497	
	Tier 2 Respiratory protection (95%)			0.0098# 0.0097¤	328# 323¤	No
	Tier 2 Protective gloves (95%)			0.00915# 0.00597¤	305# 199¤	No
	Tier 2 Respiratory protection (95%) and protective gloves (95%)			0.00090# 0.00075¤	30# 25¤	Yes

Inhalation assessed with MEASE model
¤ Inhalation assessed with TNsG model 5

12.3.3 Local effects

Local effects are not expected.

12.3.4 Conclusion

All PTs: The risk for industrial workers when mixing and loading the active substance during the formulation of polymers is acceptable if they wear appropriate respiratory protective equipment and protective gloves.

12.4 PROFESSIONAL USES

12.4.1 Systemic effects

Task/ Scenario	**Tier**	**Systemic NOAEL mg/(kg bw * d)**	**$AEL_{long-term}$ mg/(kg bw * d)**	**Estimated uptake mg/(kg bw * d)**	**Estimated uptake/ AEL (%)**	**Acceptable (yes/no)**
Scenario 2 – spray application	Tier 1	6	0.003	2.82	94052	No
	Tier 2 Hands inside gloves and body protected with overall (95% protection), 95% reduction due to use of respiratory protection			0.112	3725	No
Scenario 3.1 – brush and roll application	Tier 1			0.40	13413	No
	Tier 2 Hands inside gloves and 95% body exposure reduction using impermeable coverall			0.075	2504	No

Scenario 4 – joint sealant application	Tier 1			0.625	62500	No
Assessment based on silver ions						
		Systemic NOAEL mg/(kg bw * d) silver ions	$AEL_{long-term}$ µg/(kg bw * d) silver ions	Estimated uptake µg/(kg bw * d) silver ions		
Scenario 4 – joint sealant application	Tier 2 Silver migration rate	0.09	0.045	0.001	2.22	Yes

12.4.2 Local effects

Local effects are not expected.

12.4.3 Conclusion

PTs 2, 7: The risks for professionals when applying paints by spraying, brushing or rolling are not acceptable. Personal protective equipment is not sufficient to mitigate these risks.

PT 7: The risk for professionals manually applying sealants is acceptable without personal protection, assuming that exposure is limited by the release rate of silver from the sealant.

All PTs: The risk for professionals handling treated articles is acceptable without personal protection, assuming that exposure is limited by the release rate of silver from the treated article. This risk is covered by the consumer exposure scenario.

12.5 NON-PROFESSIONAL USERS

12.5.1 Systemic effects

Task/ Scenario	**Tier**	**Systemic NOAEL** mg/(kg bw * d)	**$AEL_{medium-term}$** mg/(kg bw * d)	**Estimated uptake** mg/(kg bw * d)	**Estimated uptake/ AEL** (%)	**Acceptable** (yes/no)
Scenario 3.2 – brush and roll application	Tier 1	30	0.01	0.15	1500	No

PT 2, 7: The risks for non-professionals when applying paints by brushing or rolling are not acceptable.

PT 7: The manual application of sealants by non-professionals is covered by the scenario for professionals, since all input values are the same for professionals and non-professional. Therefore, if the risk is acceptable for professionals, it will also be acceptable for non-professionals.

12.6 SECONDARY (INDIRECT) EXPOSURE AS A RESULT OF USE

Concept of multiple exposure

The concept was already presented in the CAR for silver zinc zeolite and agreed by the technical Meeting (TM IV 2013).

Silver zeolite is incorporated into the matrix of a range of polymers rubbers and coatings. The number of possible applications is large – and so is the number of possible ways by which people can become exposed to silver ions. Applications mentioned in the dossier, for the respective product types, are: Sanitary items, personal care items, air conditioning parts, polymer coatings, kitchen utensils, food containers, food packaging, polymer coatings, adhesives, sealants, textiles, rubber, leather.
It is probable that a person becomes exposed to silver simultaneously from using several of the above mentioned articles treated with the actual active substance. Additionally, the person may become exposed to silver from a variety of other biocidal products, in addition to treated polymer articles, such as treated swimming pool water or hand disinfection, as well as from non-biocidal uses such as cosmetics, medical products or food additives. However, these additional potential sources of exposure are not possible to include in the risk assessment under the BPR:

While a cumulative exposure assessment of the different uses of silver zeolite should be attempted, it is, however, not manageable to take into account all possible exposure situations, considering the variety of use situations described in the dossiers and the variety of treated items, not to mention all possible combinations of these.
The eCA therefore selected examples of critical use situations that each will probably give rise to the highest exposure to silver ions within a certain use pattern, as presented in the scenarios
The eCA finds it likely that a person may become exposed to silver from several uses simultaneously during a single day or during many days of life. Some articles may be used every day while others are used much more seldom. The aggregated daily dose will be highly variable.
The challenge is to quantify this cumulative exposure. Simple addition of several worst cases is expected to result in an unrealistically high exposure estimate. Instead, as a simple and rough approach, it is suggested to compare acute exposure scenario outcomes with the long-term AEL. The rationale behind is that a consumer may become exposed to silver from different use-related sources during different days. Therefore, despite that each of these exposure events may be an acute scenario, the multiple uses of silver in reality results in repeated exposure to silver. By this way, the repetitive cumulative nature of consumer exposure to silver-treated articles is reflected. The suggested approach avoids addition of several exposures, being acute or repeated. Neither does it account for several acute scenarios occurring simultaneously at the same day. However, since toxic effects from silver are observed after chronic exposure, a risk assessment from a single acute exposure is not very relevant.
To summarise the proposed approach, no acute scenario should exceed the long-term AEL at any given day.
Above this, repeated exposure from several uses within the same use pattern can be expected occasionally, which is assumed to be covered by the worst-case nature of the assumption of repetitive acute exposures. The eCA does not find it meaningful to add exposure estimates from several uses, because each single estimate is already conflicted with a high degree of uncertainty.

12.6.1 Systemic effects

Summary table: acute systemic secondary exposure of the general public								
Exposure scenario			**Tier**	**Systemic NOAEL, long-term**	**AEL, long-term**	**Estimated total uptake**	**Estimated uptake/ AEL**	**Acceptable**
				mg Ag/kg bw/d	µg/kg bw/d	µg/kg bw/d	(%)	(yes/no)
5 Dermal exposure to treated polymer: direct contact with human skin	**5.1** Small-scale	Adult	2	0.09	0.045	0.00075	1.66	yes
		Child	2	0.09	0.045	0.00098	2.17	yes
		Toddler	2	0.09	0.045	0.00126	2.80	yes
		Infant	2	0.09	0.045	0.00134	2.99	yes
	5.2 Medium scale	Adult	2	0.09	0.045	0.016	36	yes
		Child	2	0.09	0.045	0.041	91	yes
		Toddler	2	0.09	0.045	0.066	146	no
		Infant	2	0.09	0.045	0.082	182	no
	5.3 Large-scale	Adult	2	0.09	0.045	1.4	3165	no
		Child	2	0.09	0.045	2.0	4404	no
		Toddler	2	0.09	0.045	2.5	5491	no
		Infant	2	0.09	0.045	2.6	5863	no
6 Oral exposure to treated polymer: hand-to-mouth contact	Toddler or infant crawling on floor	Toddler	2	0.09	0.045	0.015	34	yes
		Infant	2	0.09	0.045	0.016	36	yes
7 Oral exposure to treated polymer: taking into mouth	**7.1** Small-scale	Adult	2	0.09	0.045	0.0006	1.3	yes
		Child	2	0.09	0.045	0.0014	3.2	yes
		Toddler	2	0.09	0.045	0.0017	3.8	yes
	7.2 A) Large-scale for infants and toddlers	Toddler	2	0.09	0.045	0.015	34	yes
		Infant	2	0.09	0.045	0.027	60	yes
	7.2 B) Large-scale for children and adults	Adult	2	0.09	0.045	0.007	16	yes
		Child	2	0.09	0.045	0.019	41	yes
8 Oral exposure to treated textile: taking into mouth	Textile taken into mouth by infants or toddlers	Toddler	2	0.09	0.045	0.062	139	no
		Infant	2	0.09	0.045	0.027	59	yes
9 Dermal exposure to treated textile: direct contact with human skin	**9.2** Small-scale	Adult	2	0.09	0.045	0.99	2203	no
		Child	2	0.09	0.045	1.33	2961	no
		Toddler	2	0.09	0.045	1.52	3369	no
		Infant	2	0.09	0.045	1.62	3597	no
	9.3 Textile handling	Adult	2	0.09	0.045	0.34	757	no
		Child	2	0.09	0.045	0.45	991	no
		Toddler	2	0.09	0.045	0.57	1275	no

Combined scenarios

The combination of the scenarios shown above has already been covered by the concept of multiple exposure pattern, i.e. comparing short-term exposure with long-term AEL. This concept is described in chapter 12.6.

12.6.2 Local effects

Local effects are not expected.

12.6.3 Conclusion

PT 4: The risk from indirect exposure using treated items is acceptable, assuming that exposure only will be small-scale.

PT 2, 7: The risk for toddlers or infants crawling on floor is acceptable. However, medium-scale exposure might lead to unacceptable risk for toddlers and infants. Small scale dermal exposure does not pose unacceptable risk to humans.

12.7 INDIRECT EXPOSURE VIA FOOD

12.7.1 Systemic effects

Summary table: indirect exposure via food						
PT 4						
Exposure scenario		**Systemic NOAEL**	**AEL**	**Estimated oral uptake**	**Estimated uptake/ AEL**	**Acceptable**
		mg Ag^+ eq/kg bw/d	µg/kg bw/d	µg/kg bw/d	(%)	(yes/no)
Migration into food simulant (3% acetic acid)	Adult	0.09	0.045	0.12-2.1	300-4580	no
	Child	0.09	0.045	0.34-5.2	752-11498	no
	Toddler	0.09	0.045	0.81-12	1798-27479	no
	Infant	0.09	0.045	1.0-15	2248-34349	no
Preservation of water filter	Adult	0.09	0.045	0.018	40	yes
	Child	0.09	0.045	0.022	49	yes
	Toddler	0.09	0.045	0.034	75	yes
	Infant	0.09	0.045	0.075	167	no

12.7.2 Local effects

Local effects are not expected.

12.7.3 Conclusion

PT 4: Based on migration data into food simulant (3% acetic acid), unacceptable risks to consumers using treated articles (including surfaces) in contact with food cannot be excluded.
The risk for consumers drinking water that has passed a filter treated with silver zeolite is acceptable for adults, children and toddlers. It is not acceptable for infants.

12.8 PRODUCTION / FORMULATION OF ACTIVE SUBSTANCE

According to the applicant, the active substance is not produced in the EU or EES.

12.9 AGGREGATED EXPOSURE

The combination of the scenarios shown above has already been covered by the concept of multiple exposure pattern, i.e. comparing short-term exposure with long-term AEL. This concept is described in chapter 12.6.

13 RISK CHARACTERISATION FOR THE ENVIRONMENT

The environmental risk assessment is carried out for silver, since it is the only environmentally relevant constituent of the active compound.

13.1 ATMOSPHERE

Silver emissions to atmosphere are negligible.

13.2 SEWAGE TREATMENT PLANT (STP)

Summary table on calculated PEC/PNEC values		
$PNEC_{STP}$ [mg/L (estimated total silver)] =	0.009	
Scenario	PEC_{STP}	$PEC/PNEC_{stp}$
	[mg/L]	
2.1 – Floor covering	1.78E-08	1.98E-06
2.2 – Treated articles – service life	3.60E-08	4.00E-06
2.3 – Polymer formulation	4.28E-06	4.76E-04
4.1 – Polymer formulation	4.28E-06	4.76E-04
4.2 – Treated articles – service life	3.60E-08	4.00E-06
7.1 – Polymers used on infrastructure		
City scenario		
Sealants indoor, application, amateur	3.45E-06	3.83E-04
Sealants indoor, application, professional	2.07E-06	2.30E-04
Sealants indoor, service-life, 100% leaching	7.56E-05	8.41E-03
Sealants indoor, service-life, leaching rate	9.86E-08	1.10E-05
7.2 – Polymer formulation	4.28E-06	4.76E-04
7.3 – Treated articles – service life	3.60E-08	4.00E-06
Aggregated exosure	*See chapter 13.7*	

Conclusion: No unacceptable risks to sewage treatment processes were identified for the intended uses.

13.3 AQUATIC COMPARTMENT

Summary table on calculated PEC/PNEC values for freshwater				
$PNEC_{water}$ [mg/L (dissolved silver)] =	0.000008			
$PNEC_{sediment}$ [mg/kg_{wwt}] =	0.00958			
Scenario	PEC_{water}	$PEC/PNEC_{water}$	PEC_{sed}	$PEC/PNEC_{sed}$
	[mg/L]			
2.1 – Floor covering	7.23E-10	8.92E-05	1.55E-05	1.62E-03
2.2 – Treated articles – service life	1.70E-09	2.13E-04	3.70E-05	0.0039
2.3 – Polymer formulation	1.71E-07	0.021	3.72E-03	0.39
4.1 – Polymer formulation	1.71E-07	0.021	3.72E-03	0.39
4.2 – Treated articles – service life	1.70E-09	2.13E-04	3.70E-05	0.0039
7.1 – Polymers used on infrastructure				

City scenario				
Sealants indoor, application, amateur	1.38E-07	0.017	3.00E-03	0.31
Sealants indoor, application, professional	8.28E-08	0.010	1.80E-03	0.19
Sealants indoor, service-life, 100% leaching	3.03E-06	0.38	0.066	6.9
Sealants indoor, service-life, leaching rate	3.94E-09	4.93E-04	8.56E-05	0.0090
7.2 – Polymer formulation	1.71E-07	0.021	3.72E-03	0.39
7.3 – Treated articles – service life	1.70E-09	2.13E-04	3.70E-05	0.0039
Aggregated exosure	*See chapter 13.7*			

Conclusion: No unacceptable risks to aquatic environment were identified for the intended uses.

13.4 TERRESTRIAL COMPARTMENT

Calculated PEC/PNEC values		
$PNEC_{soil}$ [mg/kg_{wwt}] =	0.0056	
Scenario	PEC_{soil} [mg/kg_{wwt}]	$PEC/PNEC_{soil}$
2.1 – Floor covering	6.58E-06	0.0012
2.2 – Treated articles – service life	1.34E-05	0.0024
2.3 – Polymer formulation	1.58E-03	0.28
4.1 – Polymer formulation	1.58E-03	0.28
4.2 – Treated articles – service life	1.34E-05	0.0024
7.1 – Polymers used on infrastructure		
City scenario		
Sealants indoor, application, amateur	1.27E-03	0.23
Sealants indoor, application, professional	7.64E-04	0.136
Sealants indoor, service-life, 100% leaching	2.79E-02	5.0
Sealants indoor, service-life, leaching rate	3.64E-05	0.0065
7.2 – Polymer formulation	1.58E-03	0.28
7.3 – Treated articles – service life	1.34E-05	0.0024
Aggregated exosure	*See chapter 13.7*	

Conclusion: Based on the available migration data, the use of the product does not show unacceptable risk to the soil environment.

13.5 GROUNDWATER

There is no maximum permissible concentration laid down by Directive 98/83/EC for silver.

Calculated groundwater PEC values range from $3.8 * 10^{-8}$ to $4.5 * 10^{-6}$ mg/L.

The following calculation shows that the maximum permissible concentration in groundwater of 0.1µg/L (according to Drinking Water Directive 98/83/EC) will not be exceeded as long as the risk for soil living organisms is acceptable:

We calculate the groundwater concentration at the maximum soil concentration that still would lead to acceptable risk (i.e. the PNEC soil) using equations 70 and 71 in the Vol. IV Part B (version 2.0, October 2017)

$PEC_{soil} = PNEC_{soil} = 0.0056$ mg/kg $_{wet\ weight}$

$RHO_{soil} = 1700$ kg * m^{-3}

$K_{soil\text{-}water} = 597$

$PEC_{groundwater} = PEC_{porewater} = PEC_{soil} * RHO_{soil} * K_{soil\text{-}water}^{-1} * 0.001$

$= 0.000016$ mg * L^{-1}

Using the ADI for silver derived in this report of 0.9 µg/(kg x d) and the assumption of a toddler weighing 10 kg drinking 1 litre water per day, the toxicologically acceptable limit would be 0.009 mg/L, which is above the trigger value and above estimated groundwater concentrations – as long as risk for soil living organisms is acceptable. Thus, no unacceptable risk for human health from drinking water extracted from groundwater is expected.

13.6 PRIMARY AND SECONDARY POISONING

13.6.1 Primary poisoning

Primary poisoning is not expected due to the described use patterns of silver compounds.

13.6.2 Secondary poisoning

The standard concept of assessing potential for bioaccumulation with BCF factor is not applicable for this inorganic metal compound. Trophic transfer can be an important route of exposure, but evidence of significant biomagnification is lacking. This has already been discussed in chapter 4.1.3.
Since silver binds strongly to sediments and particulate matter, the most likely risk for secondary poisoning arises from the transfer from sediment via sediment-living organisms to a predator. A food chain scenario with potentially high risk to top predators includes a filtrating or suspension feeding sediment-associated invertebrate (for example a lugworm or a mussel) eaten by a bird or mammal. We conducted an estimate based on available literature data on transfer of silver from sediments to invertebrates. Reported transfer factors organism/sediment are below 1 with the exemption of a study by Garnier Laplace 1992, reporting a factor of 1.9 (wet weight to wet weight) for gammarids after ingesting sediment particles (Ratte 1999; IIIA 7.4.2-01; Garnier-Laplace et al 1992). This factor is used as a kind of Biota Sediment Accumulation Factor (BSAF). The $PNEC_{oral}$ is divided by this factor to derive a $PNEC_{sediment}$.

For a water bird eating a sediment-living prey, the PNEC is calculated as follows:
$PNEC_{oral} = LC_{50,bird}/AF_{oral}$
$LC_{50,bird} > 76$ mg_{Ag}/kg (nominal silver)
$AF_{oral} = 3000$ (Table 26 in Vol. IV Part B)
$PNEC_{oral} = 25.3$ µg/kg

$PNEC_{sed}$ = $PNEC_{oral}$/BSAF
BSAF = 1.9
$PNEC_{sed}$ > 13.3 µg/kg_{wwt}

Using the same approach for a mammal as predator the calculations are as follows:
$PNEC_{oral}$ = $NOEC_{mammal}$/AF_{oral}
$NOEC_{mammal}$ = 3 mg_{Ag}/kg (IIIA 6.5 (06) (1992b)); silver ion equivalents calculated, maximum 42% of silver available, see background information in chapter 3)
AF_{oral} = 30 (Table 26 in Vol. IV Part B)
$PNEC_{oral}$ = 100 µg/kg

$PNEC_{sed}$ = $PNEC_{oral}$/BSAF
BSAF = 1.9
$PNEC_{sed}$ = 53 µg/kg_{wwt}

Conclusion: The $PNEC_{sed}$ via the food chain is higher than the $PNEC_{sed}$ derived for sediment living organisms (9.58 µg/kg_{wwt}). Thus, it can be concluded that if risk for sediment-living organisms is acceptable, risk for predating birds or mammals will also be acceptable.

Another emission route, is the emission via active sludge to soil (after 10 years of application). However, there is no evidence for bioaccumulation in terrestrial animals (see chapter 4.1.3.6).

13.7 AGGREGATED EXPOSURE (COMBINED FOR RELEVANT EMMISSION SOURCES)

A considerable part of silver used in society is covered by other regulatory areas. However, the biocidal uses of silver-containing active substance have a specific emission pattern. An aggregated risk assessment is therefore appropriate, in line with the decision tree in Guidance Vol. IV Part B chapter 4.7.

The only consumption-based scenario is floor covering. Anyhow, it would not be appropriate to sum tonnage-based and consumption-based scenarios, because the tonnage data include this application.
All other scenarios are each based on the total amount of tonnage for the active substance in Europe. Therefore, aggregated exposure assessment is not applicable. However, aggregated exposure assessment is needed for all silver-containing active substances with similar exposure patterns. This is presented in a separate document (see also chapter 13.8).

Note, that the exposure estimates are made based on the tonnage data provided by the applicant for the amount of biocidal product/substance placed on the EU market. This includes the product used in treated articles imported into the EU.

13.8 AGGREGATED (CUMULATIVE) EXPOSURE OR SILVER-CONTAINING ACTIVE SUBSTANCES – REGIONAL

Silver is released the environment from treated articled that are treated with a number of different silver-containing active (SCAS) substances.
BPR art 8.3 obliges the eCA to assess cumulative exposure: "Where the evaluating competent authority considers that there are concerns for human health, animal health or the

environment as a result of the cumulative effects from the use of biocidal products containing the same or different active substances, it shall document its concerns in accordance with the requirements of the relevant parts of Section II.3 of Annex XV to Regulation (EC) No 1907/2006 and include this as part of its conclusions.

An exposure assessment combining cumulative releases from all SCAS and product types is presented in a separate document.

14 RISK CHARACTERISATION FOR THE PHYSICO-CHEMICAL PROPERTIES

Silver zeolite is the assigned generic name for zeolites (sodium alumino silicate), in which sodium-ions have been exchanged with silver and additional ammonium ions (see the Confidential Appendix for the exact composition of the representative silver zeolite). Based on the nature of the substance it can be concluded that silver zeolite is not flammable, explosive or oxidizing and that it is not reactive towards packaging material.

Hereby, there are no hazards identified based on the physico-chemical properties of the representative silver zeolite included in this CAR or for a hypothetical silver zeolite conforming to the generic identity details given in Section 1.

Agion Antimicrobial Type LGK
The representative biocidal product consists of 100% of silver zeolite. As for the active substance above it can thus be concluded that are no hazards identified in relation to the physical and chemical properties of the biocidal product.

15 MEASURES TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

15.1 RECOMMENDED METHODS AND PRECAUTIONS CONCERNING HANDLING, USE, STORAGE, TRANSPORT OR FIRE

Hazards to Humans:
Harmful if inhaled or absorbed through skin. Causes moderate eye irritation. Avoid breathing dust. Avoid contact with skin, eyes or clothing. Wear goggles or face shield and rubber gloves when handling the dry powder. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash clothing before reuse.
Storage and Disposal:
Do not contaminate water, food or feed by storage and disposal.
Pesticide Disposal:
Do not store in areas accessible to children. Keep product dry and containers covered during storage; store below 130°F.

15.2 SPECIFIC TREATMENT IN CASE OF AN ACCIDENT

The following First Aid statements are provided on the label:
If on skin or clothing:
• Take off contaminated clothing.
• Rinse skin immediately with plenty of water for 15 – 20 minutes.
• Call a poison control center or doctor for treatment advice.
If in eyes :
• Hold eye open and rinse slowly and gently with water for 15 – 20 minutes.
• Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.
• Call a poison control center or doctor for treatment advice.
If inhaled:
• Move person to fresh air.
• If person is not breathing, call emergency number or an ambulance, then give artificial respiration, preferably by mouth-to-mouth, if possible.
• Call a poison control center or doctor for further treatment advice.
If swallowed:
• Call poison control center or doctor immediately for treatment advice.
• Have person sip a glass of water if able to swallow.
• Do not induce vomiting unless told to do so by the poison control center or doctor.
• Do not give anything by mouth to an unconscious person.
Have the product container or label with you when calling a poison control center or doctor, or going for treatment.

15.3 IDENTITY OF RELEVANT COMBUSTION PRODUCTS IN CASES OF FIRE

The biocidal product has no capacity to initiate or support combustion. All of its constituents are inorganic and none is pyrophoric. The zeolite matrix is essentially mineral in nature.

15.4 PROCEDURES FOR WASTE MANAGEMENT OF THE BIOCIDAL PRODUCT

Container Disposal:
Inner Plastic Bag: Completely empty plastic bag into application equipment. Then dispose of empty bag in a sanitary landfill or by incineration, or, if allowed by appropriate governmental authorities, by burning. If burned, stay out of smoke. Outer Steel Can: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by appropriate governmental authorities.
Pesticide Disposal:
Wastes from the use of this product may be disposed of on site or at an approved waste disposal facility.

15.5 POSSIBILITY OF DESTRUCTION OR DECONTAMINATION FOLLOWING RELEASE IN OR ON THE FOLLOWING: AIR, WATER (INCLUDING DRINKING WATER) AND SOIL

The possibilty of destruction or decontamination following the release of the Agion Antimicrobial Type LGK in the environment is unlikely.
Disposal of unused portions of the Agoion Antimicrobial Type LGK is unlikely, because the product is quite expensive. Small amounts can be disposed of as hazardous waste, so that any small amounts of silver eventually released through ion exchange are contained. The zeolite structure itself is essentially mineralic, and expected to be stable indefinitely. If the structure disintegrates, it will form silica, alumina, and alumina-silicates, all of which are naturally occurring.
Agion Antimicrobial Type LGK is intrinsically stable and nonreactive, no hazard develops even if a storage drum comes into contact with water or fire. In either case no immediately hazardous material is released. Spilled solid can be swept up and discarded (see above). Spilled solid that has been moistened with water can be scooped up and discarded in the same way. Water rinses of cleaned-up areas can be disposed of in sanitary or storm sewers, because such water will contain at most only trace levels of silver ions.

Part D: Appendices

Appendix I: List of endpoints

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

Active substance (ISO Name)	No ISO Name available. The name silver zeolite is used throughout the CAR.
Product-type	2, 4, 7 and 9

Identity

Chemical name (IUPAC)	Silver zeolite (Zeolite, LTA[28] framework type, ion-exchanged with silver and ammonium ions)
Chemical name (CA)	Zeolites, Ag[29]
CAS No	130328-18-6[30]
EC No	Not assigned
Other substance No.	Not assigned
Minimum purity of the active substance as manufactured (g/kg or g/l)	99% (on a dry weight basis)
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Arsenic, CAS-No.: 7440-38-2 Max. 26 ppm (mg/kg)
Molecular formula	Generic molecular formula excluding the ratio of the elements and additional ions which are considered confidential: $Ag_x\ Na_y\ (NH_4)_z\ (H_2O)_m\ [Al_{12}Si_{12}O_{48}]$ **– LTA*** * Linde Type A
Molecular mass	No data available for the active substance itself.

[28] The framework type is a crucial part of the identity. A silver zeolite with a different framework-type would not be considered the same substance.

[29] The CAS-No/CA-name is broader than specified by the IUPAC chemical name that is used for this entry. It has been agreed at WG V 2017 that the CAS-No/CA-name can still be used as an identifier.

	Calculated molar mass for the general formula for zeolite A $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]$ x 27 H_2O: 2190 g/mol.
Structural formula	Not applicable

Physical and chemical properties

Melting point (state purity)	No data for silver zeolite – relies on read-across to data on silver zinc zeolite and silver copper zeolite indicating a melting point >350°C. Due to the similarities of the materials (inorganic crystalline solids), silver zeolite complying with the generic definition is anticipated to have a melting point >>350°C.
Boiling point (state purity)	Not relevant due to the high melting point
Thermal stability / Temperature of decomposition	Based on structure and experience in use it can be concluded that silver zeolite is thermally stable and does not form dangerous substances on heating.
Appearance (state purity)	No data for silver zeolite - relies on read-across to data on silver zinc zeolite which is a white odourless dry powder. Due to the similarities of the materials the data is considered representative for silver zeolite complying with the generic definition.
Relative density (state purity)	No data presented – not considered required since this is not a crucial parameter.
Surface tension (state temperature and concentration of the test solution)	For the group of silver zeolites complying with the generic definition: Not relevant as the substance is not soluble in water and as the material only releases inorganic ions in water.
Vapour pressure (in Pa, state temperature)	For the group of silver zeolites complying with the generic definition: Not volatile (inorganic high molecular weight crystalline solid with melting point >>300 °C).
Henry's law constant (Pa m^3 mol^{-1})	For the group of silver zeolites complying with the generic definition: Not applicable as the substance is neither volatile nor soluble in water
Solubility in water (g/l or mg/l, state temperature)	The substance itself is not soluble in water.

	Under various conditions using a loading of 50 mg Ag/l (based on Agion Antimicrobial Type LGK): Distilled water: max. 0.03 mg Ag/l (0.07%), pH: 6-9 Phosphate buffer at 37 °C (physiological conditions): 9-22 mg Ag/l (16-41%), pH 4.5-4.9 6.7-8.1 mg Ag/l (13-15%), pH 8
Solubility in organic solvents (in g/l or mg/l, state temperature)	No data for silver zeolite - relies on read-across to data on silver copper zeolite which was soluble at less than 10 g/l in: n-heptane xylene ethyl acetate acetone n-octanol 1,2-dichloroethane Due to the similarities of the materials (i.e inorganic crystalline solids) silver zeolite complying with the generic definition is also not soluble in organic solvents.
Stability in organic solvents used in biocidal products including relevant breakdown products	For the group of silver zeolites complying with the generic definition: Not relevant as the substance is not formulated in organic solvents.
Partition coefficient (log P_{OW}) (state temperature)	For the group of silver zeolites complying with the generic definition: Not applicable to an inorganic crystalline solid which is neither soluble in water nor in organic solvents.
Dissociation constant	For the group of silver zeolites complying with the generic definition: Not relevant as the substance does not contain ionisable functional groups.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	For the group of silver zeolites complying with the generic definition: Not relevant as UV-VIS cannot be used as a tool for structural interpretation of the substance.

Flammability or flash point	The material has no capacity to initiate or support combustion; all components are inorganic and non-pyrophoric. Based on the structure and experience in use it can be concluded that silver zeolite is not flammable. This is an acceptable waiver for an inorganic substance under CLP.
Explosive properties	Silver zeolite complying with the generic definition does not contain any chemical groups associated with explosive properties (valid data waiver under CLP).
Oxidising properties	Data lacking – not required (based on the structure, physical chemical properties and experience in use the substance is not anticipated to be oxidizing but information not sufficient as a waiver under CLP).
Auto-ignition or relative self ignition temperature	Auto-ignition / relative self-ignition: Data lacking (not anticipated to self-ignite < 400°C. The material has no capacity to initiate or support combustion; all components are inorganic and non-pyrophoric). Self-heating: Silver zeolite is not a self-heating substance (negative results in a 25 mm and a 100 mm sample cube at 140°C).

Classification and proposed labelling

with regard to physical hazards	None
with regard to human health hazards	Repr 2, H361d[30]
with regard to environmental hazards	Aquatic Acute 1, M=100 Aquatic Chronic 1, M=100

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	No specific method for silver zeolite as such ICP-OES for the quantification of major elements (including silver) and elements treated as impurities (including potential heavy metals).

[30] There is no substance-specific data available for this hazard class hence it is not possible to conclude whether or not the active substance fulfils criteria for classification. However, based on the information available for each constituent of silver zeolite, it is reasonable to assume that silver zeolite fulfils criteria for classification Repr. 2. This is further discussed in the subsection of part A, section 3.

Impurities in technical active substance (principle of method)	See technical active substance entry above

Analytical methods for residues

Soil (principle of method and LOQ)	Determination of silver; see LoEP of silver core CAR
Air (principle of method and LOQ)	Not required as silver zeolite is not volatile and it is not used in spraying applications
Water (principle of method and LOQ)	Determination of silver see LoEP of silver core CAR
Body fluids and tissues (principle of method and LOQ)	Not required as silver zeolite is not proposed to be classified as T or T+ for acute effects
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Determination of silver; see LoEP of silver core CAR
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	No substance-specific information available. Oral absorption of silver ions released from the active substance is estimated to be 5% based on literature data indicating a cumulative excretion of less than 10% in mice, rats, dogs and monkeys 2 days after an oral dose of silver nitrate (Furchner et al. 1968).
Rate and extent of dermal absorption*:	No substance-specific information available. Dermal absorption of the active substance and of silver ions is assumed to be 5% based on literature data on silver nitrate (Skog and Wahlberg, 1963).
Distribution:	No substance-specific information available. Based on literature data, silver absorbed following intramuscular administration of silver nitrate is widely distributed in the rat. Highest amounts found in the GI tract followed by liver, blood, kidney, skin, muscle, bone, heart, lungs and spleen (Scott and Hamilton, 1950).

Potential for accumulation:	Silver accumulates in tissues and organs. Visible deposition of silver in human skin is a condition known as argyria
Rate and extent of excretion:	No substance-specific information available. Literature data indicate a cumulative excretion of less than 10% of orally administered silver nitrate in mice, rats, dogs and monkeys after 2 days (Furchner et al. 1968). Other information available in the open literature indicate that silver absorbed from silver nitrate undergoes a first-pass effect in the liver and is excreted via biliary excretion mechanism that (at least in the rat) can be saturated (Scott and Hamilton, 1950). The amount of biliary excretion appears to vary between species. According to a study in rat, silver is conjugated to glutathione prior to excretion in bile (Baldi, C. et al.). According to human data, inhaled silver is distributed to the liver. Biological half-lives of 1 and 52 days are assumed to represent rapid lung clearance by ciliary action and liver clearance respectively (Newton and Holmes (1966)).
Toxicologically significant metabolite(s)	Silver ion

* the dermal absorption value is applicable for the active substance and might not be usable in product authorization

Acute toxicity

Rat LD_{50} oral	>5000 mg/kg bw
Rat LD_{50} dermal	>5000 mg/kg bw
Rat LC_{50} inhalation	>2.05 mg/l (assumed to be the highest attainable concentration)

Skin corrosion/irritation	The active substance is not corrosive or irritating to (rabbit) skin.
Eye irritation	The active substance causes reactions in (rabbit) eyes but effects do not fulfil criteria for classification.
Respiratory tract irritation	No data
Skin sensitisation (test method used and result)	The active substance does not induce skin sensitisation reactions (LLNA, no reactions

	upon challenge with 25%, claimed to be the highest soluble concentration)
Respiratory sensitisation (test method used and result)	No data

Repeated dose toxicity

Short term

Species / target / critical effect	No substance-specific information available for silver zeolite.
Relevant oral NOAEL / LOAEL	No data
Relevant dermal NOAEL / LOAEL	No data
Relevant inhalation NOAEL / LOAEL	No data

Subchronic

Species/ target / critical effect	No substance-specific information available for silver zeolite. Rat/general pigmentation of organs and tissues
Relevant oral NOAEL / LOAEL	NOAEL: 21 mg/kg bw/d[31] $NOAEL_{silver\ ion\ equivalents}$: 0.3 mg/kg bw/d LOAEL: 214 mg/kg bw/d $LOAEL_{silver\ ion\ equivalents}$: 3 mg/kg bw/d)
Relevant dermal NOAEL / LOAEL	No data
Relevant inhalation NOAEL / LOAEL	No data

Long term

Species/ target / critical effect	No substance-specific information available for silver zeolite. Rat/general pigmentation of organs and tissues

[31] Based on data obtained with silver sodium hydrogen zirconium phosphate. The NOAEL set for silver zeolite is estimated by calculating the dose needed to achieve the silver ion concentration at the NOAEL set for silver sodium hydrogen zirconium phosphate.

Relevant oral NOAEL / LOAEL	NOAEL: 6 mg/kg bw/d[32] $NOAEL_{silver\ ion\ equivalents}$: 0.09 mg/kg bw/d LOAEL: 21 mg/kg bw/d $LOAEL_{silver\ ion\ equivalents}$: 0.3 mg/kg bw/d
Relevant dermal NOAEL / LOAEL	No data
Relevant inhalation NOAEL / LOAEL	No data

Genotoxicity

	No substance-specific information available for silver zeolite. Negative (based on data for silver zinc zeolite Type AK).

Carcinogenicity

Species/type of tumour	No substance-specific information available for silver zeolite. Based on data for silver zinc zeolite Type AK: Rat/Mice/tumours observed are not considered treatment related
Relevant NOAEL/LOAEL	Not relevant

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	No substance-specific information available for silver zeolite.
Relevant maternal NOAEL	NA
Relevant developmental NOAEL	Developmental toxicity of silver ions are covered by NOAEL set for fertility.

Fertility

Species/critical effect	No substance-specific information available for silver zeolite.Read across to data with silver zinc zeolite Type AK: Rat/offspring viability and development (reduced total pups born/litter, increased stillborn index, reduced livebirth index, reduced liveborn/litter reduced pup survival index, delay of day of sexual maturation) **Repr. 2;H361d**

[32] Based on data obtained with silver zinc zeolite Type AJ. The NOAEL set for silver zeolite is estimated by calculating the dose needed to achieve the silver ion concentration at the NOAEL set for silver zinc zeolite Type AJ.

Relevant parental NOAEL	NOAEL: <lowest dose tested (pigmentation and reduced thymus weight)
Relevant offspring NOAEL	NOAEL: <lowest dose tested (pigmentation and reduced thymus weight)
Relevant fertility NOAEL	NOAEL: 1000 ppm (109 mg/kg bw/d) $NOAEL_{silver\ ion\ equivalents}$: 1.5 mg/kg bw/d

Neurotoxicity

Species/ target/critical effect	No substance-specific data. No indications of neurotoxicity in repeated dose toxicity studies performed with different silver containing active substances.

Developmental Neurotoxicity

Species/ target/critical effect	No data.

Immunotoxicity

Species/ target/critical effect	No substance-specific data.

Developmental Immunotoxicity

Species/ target/critical effect	No data

Other toxicological studies

Human case reports describing argyria supports a human relevance of effects observed in animal studies.

Medical data

Argyria is an irreversible effect.

Summary

	Value	Study	Safety factor
$AEL_{long\text{-}term}$	0.003 mg/kg bw/d	Chronic toxicity/Carcino-genicity study with silver zinc zeolite Type AJ	100
$AEL_{medium\text{-}term}$	0.01 mg/kg bw/d	13 week study in rat with silver sodium hydrogen zir-conium phosphate	100
$AEL_{short\text{-}term}$	If needed, the short-term AEL equals the medium-term AEL.		

ADI[33]	Not relevant		
ARfD	Not relevant		
	Silver ion equivalents		
$AEL_{long-term}$	0.045 µg/kg bw/d	Rat 105 w oral with silver zinc zeolite type AgION Zeomic AJ 10N	100
$AEL_{medium-term}$	0.15 µg/kg bw/d	Rat 13 w oral with AgNaH-ZrPO4 AlphaSan RC5000	100
$AEL_{short-term}$	0.15 µg/kg bw/d	Rat 13 w oral with AgNaH-ZrPO4 AlphaSan RC5000	100
ADI	0.9 µg/kg bw/d	Rat 105 w oral with silver zinc zeolite type AgION Zeomic AJ 10N	100
ARfD	Not relevant		

MRLs

Relevant commodities	Not available

Reference value for groundwater

According to BPR Annex VI, point 68	Not available

Dermal absorption

Study (*in vitro/vivo*), species tested	No data, see information above
Formulation (formulation type and including concentration(s) tested, vehicle)	The representative formulation Agion Antimicrobial Type LGK is identical to the active substance
Dermal absorption values used in risk assessment	5%

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

[33] If residues in food or feed.

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature) pH 5 pH 9 Other pH: *[indicate the value]* Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Not applicable as silver zeolites consist of chemical elements that cannot be degraded.
Readily biodegradable (yes/no) Inherent biodegradable (yes/no) Biodegradation in freshwater Biodegradation in seawater	Not applicable as silver zeolites consist of chemical elements that cannot be degraded (set to "no" in environmental exposure modelling)
Non-extractable residues	Not applicable
Distribution in water / sediment systems (active substance)	Silver is considered the major active and relevant specie. The free Ag+ is considered the mobile and ecotoxicologically significant substance.
Distribution in water / sediment systems (metabolites)	Although silver is unable to degrade, it is able to interact with a wide array of natural materials so that the vast majority of silver in the environment is rapidly bound to mineral particles, precipitated as insoluble salts, or bound to organic matter.

Route and rate of degradation in soil

Mineralization (aerobic) Laboratory studies (range or median, with number of measurements, with regression coefficient) DT_{50lab} (20°C, aerobic): DT_{90lab} (20°C, aerobic): DT_{50lab} (10°C, aerobic): DT_{50lab} (20°C, anaerobic): degradation in the saturated zone: Field studies (state location, range or median with number of measurements) DT_{50f}: DT_{90f}: Anaerobic degradation	Not applicable as silver zeolite consist of chemical elements that cannot be degraded.

Soil photolysis Non-extractable residues Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	
Soil accumulation and plateau concentration	As silver will be readily retained, strongly bound and do not degrade in soil the elements will accumulate in soil over time.

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Not applicable as silver zeolites are inorganic compounds. Constants related to silver used for risk assessment, see LoEP of silver core CAR.

Fate and behaviour in air

Direct photolysis in air Quantum yield of direct photolysis Photo-oxidative degradation in air Volatilization	Not applicable as silver zeolites are not volatile and consist of chemical elements that cannot be degraded.

Reference value for groundwater

According to BPR Annex VI, point 68	Not available

Monitoring data, if available

Soil (indicate location and type of study) Surface water (indicate location and type of study) Ground water (indicate location and type of study) Air (indicate location and type of study)	Monitoring data for silver are available, but these cannot be specifically linked to the use of silver zeolite or generally silver as a biocide.

Chapter 5: Effects on Non-target Species

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

Species	Time-scale	Endpoint	Toxicity
Fish			

Oncorhynchus mykiss	51-77d	Larval growth	NOEC: 0.08 µg/L Ag (geometric mean of 3 studies, measured dissolved silver)
Invertebrates			
Ceriodaphnia dubia	10d	Survival and re-production	NOEC: 0.53 µg/L Ag (measured dissolved silver)
Algae			
Pseudokirchneriella subcapitata	72h	Growth rate	NOE_rC: 0.75 µg/L E_rC_{50}: 4.0 µg/L
Microorganisms			
-	-	-	-

Effects on earthworms or other soil non-target organisms

Acute toxicity to -	-
Reproductive toxicity to *Eisenia fetida*	56d NOEC: 10.43 mg/kg silver in dry soil

Effects on soil micro-organisms

Nitrogen mineralization	NOEC: 1.02 mg/kg silver in dry soil
Carbon mineralization	NOEC: 0.32 mg/kg silver in dry soil

Effects on terrestrial plants

Allium cepa, Phaseolus vulgaris	NOEC: <0.1 mg/kg silver in dry soil* * inconclusive results

Effects on terrestrial vertebrates

Chronic toxicity to mammals	NOAEL: 0.09 mgAg/(kg bw * d) (silver ion equivalents calculated) NOEC: 3 mgAg/kg (silver ion equivalents calculated)
Acute toxicity to birds	NOEC (body weight): 28 mgAg/kg (nominal silver)
Dietary toxicity to birds	NOEC: 188 mgAg/kg (measured silver)
Reproductive toxicity to birds	-

Effects on honeybees

Acute oral toxicity	-
Acute contact toxicity	-

Effects on other beneficial arthropods

Acute oral toxicity	-
Acute contact toxicity	-
Acute toxicity to ……..	-

Bioconcentration

Bioconcentration factor (BCF)	Not applicable
Depration time (DT_{50})	Not applicable
Depration time (DT_{90})	Not applicable
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable

Chapter 6: Other End Points

Appendix II: Human exposure calculations

1 Uses of treated articles – information provided for silver zeolite by applicant during different stages of the evaluation

	PT2	PT4	PT7	PT9
Dossier (August 2015)	consumer items where an antimicrobial effect is desirable, for example: walls and flooring, heating, ventilation and air conditioning equipment, protective covers, waste containers, plumbing equipment (for example toilet seat or bathtub), office equipment and personal care items.	used to make or coat consumer items where an antimicrobial effect is desirable in a food/feed situation, for example: packaging, gaskets, food containers, trays and covers, food wrap, tubing, appliances, food processing equipment and utensils.	incorporated into polymers, coatings, laminates, adhesives and sealants at a maximum level of 5.0% by weight. These items may be used in a number of domestic and commercial applications.	Type LGK is incorporated into polymers and coatings at a maximum level of 0.5% by weight for use in textiles (not for apparel).
Information provided related to tonnage data (August 2015)	Example items: Wall or floor covering for use in locations where a hygienic environment is desirable. Air conditioning components where control of bacteria is necessary to maintain hygiene.	Example items: Polymer kitchen utensil to help in maintaining a hygienic surface. Water filter for control of bacteria to reduce clogging and pressure.	Example items: Protective finishes applied to foam, moulded parts, rubber sheet.	Example items: Textile/leather with increased durability claim. Rubber/polymer seals treated to protect against microbial/fungal deterioration - increase durability.
Information related to efficacy (August 2016)	i) wall or floor covering ii) air conditioning components	i) food packaging ii) food containers, tubing iii) food processing equipment iv) food utensils.	i) laminated work surface ii) paint finish	i) refrigerator seal ii) shower curtain (non-apparel)
Information related to human exposure (September 2016)	Sanitary items Personal care items Air conditioning parts Polymer coatings	Kitchen utensils Containers Packaging	Polymer coatings Adhesives Sealant	Textiles Polymer seals

2.a Migration studies provided for silver zinc zeolites and silver zeolites from polymers

SCAS	Type	Polymer type	Conc. of SCAS in polymer (nominal)	Conc. of silver in SCAS	Conc. of silver in polymer	Surface area of test item	Volume of test medium	Test medium	Measured concentration of Ag in medium		Migration rate			Measured Ag in medium	Migration rate		Test reference
														addition of 1.4% ammonia *			
			%	%	%	cm^2	L		µg * L^{-1}		ng * cm^{-2} * h^{-1}			µg * L^{-1}	ng * cm^{-2} * h^{-1}		
									0-2h	0-24h	0-2h	0-24h	2-24h	0-24h	0-24h	2-24h	
silver zinc zeolite	AJ10D	ABS	3	2,5	0,075	52	0,25	Sweat (acid)	8,9	11,9	21,4	2,38	0,66				Sciessent IIIB 6.7.1.2-07
			3	2,5	0,075	52	0,25	Sweat (alkaline)	8,5	12,3	20,4	2,46	0,83				
			3	2,5	0,075	52	0,25	Saliva	8,3	9,6	20,0	1,92	0,28				
		PC	3	2,5	0,075	52	0,25	Sweat (acid)	2,4	2,9	5,8	0,58	0,11				
			3	2,5	0,075	52	0,25	Sweat (alkaline)	1,8	2,4	4,3	0,48	0,13				
			3	2,5	0,075	52	0,25	Saliva	2,6	4,5	6,3	0,90	0,42				
		LDPE	3	2,5	0,075	54	0,25	Sweat (acid)	4,6	2,8	10,6	0,55	-0,36				Sciessent (silver zinc zeolite) IIIB 6.7.1.2-09, Sciessent (silver zeolite) IIIA 6.14-03
			3	2,5	0,075	54	0,25	Sweat (alkaline)	4,6	4,2	10,7	0,81	-0,09				
			3	2,5	0,075	54	0,25	Saliva	3,8	10,1	8,7	1,95	1,33				
		PP	0,36	2,5	0,009	94	0,003	Sweat (acid)	93	93	1,48	0,12	0,00	166	0,221	0,107	Sciessent/Ishizuka IIIB
			0,36	2,5	0,009	94	0,003	Sweat (alkaline)	75	106	1,19	0,14	0,04	145	0,193	0,102	

			0,36	2,5	0,009	94	0,003	Saliva	70	119	1,12	0,16	0,07	155	0,205	0,123	6.7.1.2-08
	Irgar-guard B5000	LDPE	0,5	4,4	0,022	52	0,0015	Sweat (acid)	35	95	0,505	0,114	0,079	170	0,204	0,177	BASF IIIB 6.7.1.2-01
			0,5	4,4	0,022	52	0,0015	Sweat (alkaline)	20	105	0,288	0,126	0,111	180	0,216	0,210	
			0,5	4,4	0,022	52	0,0015	Saliva	15	130	0,216	0,156	0,151	130	0,156	0,151	
			1	4,4	0,044	52	0,0015	Sweat (acid)	55	15	0,793	0,018	-0,052	250	0,300	0,256	
			1	4,4	0,044	52	0,0015	Sweat (alkaline)	35	155	0,505	0,186	0,157	220	0,264	0,243	
			1	4,4	0,044	52	0,0015	Saliva	15	185	0,216	0,222	0,223	198	0,238	0,240	
		PP	0,5	4,4	0,022	52	0,0015	Sweat (acid)	55	55	0,793	0,066	0,000	65	0,078	0,013	
			0,5	4,4	0,022	52	0,0015	Sweat (alkaline)	30	40	0,433	0,048	0,013	55	0,066	0,033	
			0,5	4,4	0,022	52	0,0015	Saliva	25	50	0,361	0,060	0,033	50	0,060	0,033	
			1	4,4	0,044	52	0,0015	Sweat (acid)	45	170	0,649	0,204	0,164	270	0,325	0,295	
			1	4,4	0,044	52	0,0015	Sweat (alkaline)	25	180	0,361	0,216	0,203	220	0,264	0,256	
			1	4,4	0,044	52	0,0015	Saliva	15	215	0,216	0,258	0,262	215	0,258	0,262	
		PVC	0,5	4,4	0,022	52	0,0015	Sweat (acid)	40	240	0,577	0,288	0,262	305	0,367	0,347	
			0,5	4,4	0,022	52	0,0015	Sweat (alkaline)	20	190	0,288	0,228	0,223	270	0,325	0,328	
			0,5	4,4	0,022	52	0,0015	Saliva	15	365	0,216	0,439	0,459	365	0,439	0,459	
			1	4,4	0,044	52	0,0015	Sweat (acid)	65	290	0,938	0,349	0,295	350	0,421	0,374	
			1	4,4	0,044	52	0,0015	Sweat (alkaline)	35	280	0,505	0,337	0,321	355	0,427	0,420	
			1	4,4	0,044	52	0,0015	Saliva	35	355	0,505	0,427	0,420	355	0,427	0,420	
		PA6	0,5	4,4	0,022	54	0,0015	Sweat (acid)	30	225	0,417	0,260	0,246	235	0,272	0,259	BASF IIIB

			0,5	4,4	0,022	54	0,0015	Sweat (alkaline)	20	240	0,278	0,278	0,278	250	0,289	0,290	6.7.1.2-02
			0,5	4,4	0,022	54	0,0015	Saliva	30	245	0,417	0,284	0,271	245	0,284	0,271	
			1	4,4	0,044	54	0,0015	Sweat (acid)	25	320	0,347	0,370	0,372	335	0,388	0,391	
			1	4,4	0,044	54	0,0015	Sweat (alkaline)	15	360	0,208	0,417	0,436	375	0,434	0,455	
			1	4,4	0,044	54	0,0015	Saliva	40	360	0,556	0,417	0,404	370	0,428	0,417	
		TPU	1	4,4	0,044	50	0,0015	Sweat (acid)	10	15	0,150	0,019	0,007	25	0,031	0,021	
			1	4,4	0,044	50	0,0015	Sweat (alkaline)	15	20	0,226	0,025	0,007	45	0,056	0,041	
			1	4,4	0,044	50	0,0015	Saliva	15	75	0,226	0,094	0,082	95	0,119	0,109	
		PU foam	1	4,4	0,044	11	0,003	Sweat (acid)	45	25	6,193	0,287	-0,250	35	0,401	-0,125	
			1	4,4	0,044	11	0,003	Sweat (alkaline)	45	70	6,193	0,803	0,313	80	0,917	0,438	
			1	4,4	0,044	11	0,003	Saliva	50	80	6,881	0,917	0,375	95	1,089	0,563	
silver zeolite	LGT10T	LDPE	3	5	0,15	54	0,25	Sweat (acid)	16	27,0	37,0	5,21	2,31				Sciessent (silver zeolite) IIIA 6.14-01
			3	5	0,15	54	0,25	Sweat (alkaline)	17	23,0	39,4	4,44	1,26				
			3	5	0,15	54	0,25	Saliva	17	27,0	39,4	5,21	2,10				
	Type LGK	Urethane	12,50	4,9	0,6125	52	0,39	0.8 % NaNO3	29		54,4						Sciessent (silver zeolite) IIIA 6.14-02

migration based on sample volume																	

SCAS	Type	Polymer type	Concentration of SCAS in polymer (nominal)	Conc. of silver in SCAS	Concentration of silver in polymer	Volume of test item	Volume of test medium	Test medium	Measured concentration of Ag in medium		Migration rate			Measured concentration of Ag in medium	Migration rate		
						cm^3	L		µg * L^{-1}		ng * cm^{-3} * h^{-1}				ng * cm-3 * h-1		
									0-2h	0-24h	0-2h	0-24h	2-24h	0-24h	0-24h	2-24h	
silver zinc zeolite	Irgarguard B5000	PU foam	1	4,4	0,044	2,1	0,003	Sweat (acid)	45	25	32,14	1,49	-1,30	35	2,1	-0,6	BASF IIIB 6.7.1.2-02
			1	4,4	0,044	2,1	0,003	Sweat (alkaline)	45	70	32,14	4,17	1,62	80	4,8	2,3	
			1	4,4	0,044	2,1	0,003	Saliva	50	80	35,71	4,76	1,95	95	5,7	2,9	

* addition of 1.4% ammonia to resolubilize precipitated silver chloride

Migration rates extrapolated to maximum concentration 5% (Sciessent) or 1.5% (BASF)										
SCAS	Type	Polymer type	Conc. of SCAS in polymer (nominal)	Maximum SCAS concentration in polymer	Test medium	Extrapolated migration rate				Test reference
			%	%		ng * cm-2 *h-1			addition of 1.4% ammonia ng * cm-2 *h-1	
						0-2h	0-24h	2-24h	0-24h	2-24h	
silver zinc zeolite	AJ10D	ABS	3	5	Sweat (acid)	35,7	3,97	1,09			Sciessent IIIB 6.7.1.2-07
			3	5	Sweat (alkaline)	34,1	4,11	1,38			
			3	5	Saliva	33,3	3,21	0,47			
		PC	3	5	Sweat (acid)	9,6	0,97	0,18			

			3	5	Sweat (alka-line)	7,2	0,80	0,22			
			3	5	Saliva	10,4	1,50	0,69			
		LDPE	3	5	Sweat (acid)	17,6	0,91	-0,61			Sciessent (silver zinc zeolite) IIIB 6.7.1.2-09, Sciessent (silver zeolite) IIIA 6.14-03
			3	5	Sweat (alka-line)	17,9	1,35	-0,15			
			3	5	Saliva	14,5	3,25	2,22			
		PP	0,36	5	Sweat (acid)	20,5	1,71	0,00	3,07	1,48	Sciessent/Ishizuka IIIB 6.7.1.2-08
			0,36	5	Sweat (alka-line)	16,5	1,95	0,62	2,68	1,42	
			0,36	5	Saliva	15,5	2,20	0,99	2,85	1,70	
	Irgarguard B5000	LDPE	0,5	1,5	Sweat (acid)	1,5	0,34	0,24	0,61	0,53	BASF IIIB 6.7.1.2-01
			0,5	1,5	Sweat (alka-line)	0,9	0,38	0,33	0,65	0,63	
			0,5	1,5	Saliva	0,6	0,47	0,45	0,47	0,45	
			1	1,5	Sweat (acid)	1,2	0,03	-0,08	0,45	0,38	
			1	1,5	Sweat (alka-line)	0,8	0,28	0,24	0,40	0,36	
			1	1,5	Saliva	0,3	0,33	0,33	0,36	0,36	
		PP	0,5	1,5	Sweat (acid)	2,4	0,20	0,00	0,23	0,04	
			0,5	1,5	Sweat (alka-line)	1,3	0,14	0,04	0,20	0,10	
			0,5	1,5	Saliva	1,1	0,18	0,10	0,18	0,10	
			1	1,5	Sweat (acid)	1,0	0,31	0,25	0,49	0,44	
			1	1,5	Sweat (alka-line)	0,5	0,32	0,30	0,40	0,38	
			1	1,5	Saliva	0,3	0,39	0,39	0,39	0,39	

		PVC	0,5	1,5	Sweat (acid)	1,7	0,87	0,79	1,10	1,04	
			0,5	1,5	Sweat (alka-line)	0,9	0,69	0,67	0,97	0,98	
			0,5	1,5	Saliva	0,6	1,32	1,38	1,32	1,38	
			1	1,5	Sweat (acid)	1,4	0,52	0,44	0,63	0,56	
			1	1,5	Sweat (alka-line)	0,8	0,50	0,48	0,64	0,63	
			1	1,5	Saliva	0,8	0,64	0,63	0,64	0,63	
		PA6	0,5	1,5	Sweat (acid)	1,3	0,78	0,74	0,82	0,78	
			0,5	1,5	Sweat (alka-line)	0,8	0,83	0,83	0,87	0,87	
			0,5	1,5	Saliva	1,3	0,85	0,81	0,85	0,81	
			1	1,5	Sweat (acid)	0,5	0,56	0,56	0,58	0,59	
			1	1,5	Sweat (alka-line)	0,3	0,63	0,65	0,65	0,68	
			1	1,5	Saliva	0,8	0,63	0,61	0,64	0,63	BASF IIIB 6.7.1.2-02
		TPU	1	1,5	Sweat (acid)	0,2	0,03	0,01	0,05	0,03	
			1	1,5	Sweat (alka-line)	0,3	0,04	0,01	0,08	0,06	
			1	1,5	Saliva	0,3	0,14	0,12	0,18	0,16	
		PU foam	1	1,5	Sweat (acid)	9,3	0,43	-0,38	0,60	-0,19	
			1	1,5	Sweat (alka-line)	9,3	1,20	0,47	1,38	0,66	
			1	1,5	Saliva	10,3	1,38	0,56	1,63	0,84	
	LGT10T	LDPE	3	5	Sweat (acid)	61,7	8,68	3,86			

silver zeo-lite			3	5	Sweat (alka-line)	65,6	7,39	2,10			Sciessent (silver zeolite) IIIA 6.14-01
			3	5	Saliva	65,6	8,68	3,51			
	Type LGK	Uret-hane	12,5	5	0.8 % NaNO3	21,8					Sciessent (silver zeolite) IIIA 6.14-02

migration based on sample volume											
SCAS	Type	Poly-mer type	Concentra-tion of SCAS in polymer (nominal)	Maximum SCAS con-centration in polymer	Test me-dium	Extrapolated migration rate					Test reference
						µg * L-1					
silver zinc zeo-lite	Irgar-guard B5000	PU foam	1	1,5	Sweat (acid)	48,2	2,23	-1,95	3,13	-0,97	BASF IIIB 6.7.1.2-02
				1,5	Sweat (alka-line)	48,2	6,25	2,44	7,14	3,41	
				1,5	Saliva	53,6	7,14	2,92	8,48	4,38	

* addition of 1.4% ammonia to resolubilize precipitated silver chloride

2.b Migration studies provided for silver copper zeolites in textiles

Migration per surface area														
SCAS	Type	Polymer type	Conc. of SCAS in polymer (nominal)	Conc. of silver in SCAS	Conc. of silver in polymer	Surface area of test item	Volume of test me-dium	Test medium	Measured concentration of Ag in medium		Migration rate			Test reference
			%	%	%	cm^2	L		µg * L^{-1}		ng*cm^{-2} * h^{-1}			
									0-2h	0-24h	0-2h	0-24h	2-24h	
Silver copper zeolite	AC10D	PET	1.5	3.5	0.053	26	0.25	Sweat (acidic)	1.1	1.6	5.3	0.6	0.2	Siessent (silver zeolite dossier) IIIA 6.14-03
			1.5	3.5	0.053	26	0.25	Sweat (alkaline)	<1	1.3	4.8	0.5	0.1	
			1.5	3.5	0.053	26	0.25	Saliva	<1	7.1	4.8	2.8	2.7	
			0.34	3.5	0.012	26	0.25	Sweat (acidic)	42	49	202	20	3.1	

		Not specified	0.34	3.5	0.012	26	0.25	Sweat (alkaline)	53	80	255	32	11.8	Addendum to Siessent (silver zeolite dossier) IIIA 6.14-03
			0.34	3.5	0.012	26	0.25	Saliva	50	63	240	25	5.7	

Migration per weight																	
SCAS	Type	Polymer type	Conc. of SCAS in polymer (nomi-	Conc. of silver in SCAS	Conc. of silver in polymer	Weight of test item	Volume of test medium	Test medium	Measured concentration of Ag in medium		Migration			Migration rate			Test reference
			%	%	%	g	L		µg * L^{-1}		%			% * h^{-1}			
									0-2h	0-24h	0-2h	0-24h	2-24h	0-2h	0-24h	2-24h	
Silver copper zeolite	silver copper zeolite AC10D	PET	1.5	3.5	0.053	4.7	0.25	Sweat (acidic)	1.1	1.6	0.011	0.016	0.005	0.0056	0.00067	0.00023	Siessent (silver zeolite dossier) IIIA 6.14-03
			1.5	3.5	0.053	4.7	0.25	Sweat (alkaline)	<1	1.3	0.010	0.013	0.003	0.0051	0.00055	0.00014	
			1.5	3.5	0.053	4.7	0.25	Saliva	<1	7.1	0.010	0.072	0.062	0.0051	0.00299	0.00281	
		Not specified	0.34	3.5	0.012	5	0.25	Sweat (acidic)	42	49	1.8	2.0	0.29	0.88	0.09	0.013	Addendum to Siessent (silver zeolite dossier) IIIA 6.14-03
			0.34	3.5	0.012	5	0.25	Sweat (alkaline)	53	80	2.2	3.3	1.13	1.11	0.14	0.051	
			0.34	3.5	0.012	5	0.25	Saliva	50	63	2.1	2.6	0.54	1.04	0.11	0.025	

2.c Migration from polymers into food simulants – information provided for silver zinc zeolite by applicant

Test reference	Product type	Polymer type	Concentration of SZZ in polymer	Conc. of silver in SZZ	Conc. of silver in polymer	Surface area of test item	Volume of test medium	Test medium	Exposure time	Measured concentration of Ag in medium	Migration rate
			%	%	%	cm^2	L			µg*L-1	µg*cm-2
Sciessent IIIB 6.7.1.2-01	Silver Antimicrobial Type AK	LLDPE	10	4.9	0.49	48	0.075	3% acetic acid at 40°C	0-2h	573	0.89
									2-4h	16	0.025
									4-6h	9	0.014
									0-6h	*598*	*0.93*
		LLDPE	10	4.9	0.49	48	0.075	3% acetic acid at 5°C	0-2h	450	0.70

Test reference	Product type	Polymer type	Concentration of SZZ in polymer	Conc. of silver in SZZ	Conc. of silver in polymer	Surface area of test item	Volume of test medium	Test medium	Exposure time	Measured concentration of Ag in medium	Migration rate
			%	%	%	cm^2	L			µg*L-1	µg*cm-2
									2-4h	87	0.13
									4-6h	27	0.042
									0-6h	*564*	*0.87*
Sciessent IIIB 6.7.1.2-03		PBT	10	4.9	0.51	48	0.075	3% acetic acid at 99°C	0-2h	177	0.27
									2-4h	13	0.020
									4-6h	4	0.006
									0-6h	*194*	*0.30*
Sciessent IIIB 6.7.1.2-02		PVC	10	4.9	0.48	48	0.075	3% acetic acid at 99°C	0-2h	1330	2.06
									2-4h	410	0.64
									4-6h	360	0.56
									0-6h	*2100*	*3.25*
Sciessent IIIB 6.7.1.2-04		Polystyrene	9	4.9	0.44	48	0.075	3% acetic acid at 99°C	0-2h	710	1.10
									2-4h	290	0.45
									4-6h	170	0.26
									0-6h	*1170*	*1.81*
Sciessent IIIB 6.7.1.2-05	AJ10D	Coated steel (paint coat)	7	2.5	0.18	52	0.08	3% acetic acid at 99°C	0-2h	87	0.13
									2-4h	15	0.023
									4-6h	8	0.012
									0-6h	*110*	*0.17*
		Coated steel (powder coat)	7	2.5	0.18	52	0.08	3% acetic acid at 99°C	0-2h	77	0.12
									2-4h	17	0.026
									4-6h	12	0.019
									0-6h	*106*	*0.16*
Sciessent IIIB 6.7.1.2-06	AK10D	Acrylic coating on oriented PP	10	4.9	0.49	52	0.15	3% acetic acid at 99°C	0-2h	670	1.95
									2-4h	6	0.017
									4-6h	1	0.003
									0-6h	*677*	*1.97*
Sciessent IIIB 6.7.1.2-01	Silver Antimicrobial Type AK	LLDPE	10	4.9	0.49	48	0.075	15% Ethanol at 40°C	0-2h	23	0.036
									2-4h	30	0.046
									4-6h	29	0.045
									0-6h	*82*	*0.13*
Sciessent IIIB 6.7.1.2-03		PBT	10	4.9	0.51	48	0.075	15% Ethanol at 99°C	0-2h	48	0.074
									2-4h	16	0.025
									4-6h	10	0.015
									0-6h	*74*	*0.11*
		PVC	10	4.9	0.48	48	0.075	15% Ethanol at 99°C	0-2h	200	0.31

Test reference	Product type	Polymer type	Concentration of SZZ in polymer	Conc. of silver in SZZ	Conc. of silver in polymer	Surface area of test item	Volume of test medium	Test medium	Exposure time	Measured concentration of Ag in medium	Migration rate
			%	%	%	cm^2	L			µg*L-1	µg*cm-2
Sciessent IIIB 6.7.1.2-02									2-4h	120	0.19
									4-6h	62	0.10
									0-6h	*382*	*0.59*
Sciessent IIIB 6.7.1.2-04		Polystyrene	9	4.9	0.44	48	0.075	15% Ethanol at 99°C	0-2h	180	0.28
									2-4h	110	0.17
									4-6h	27	0.042
									0-6h	*317*	*0.49*
Sciessent IIIB 6.7.1.2-05	AJ10D	Coated steel (paint coat)	7	2.5	0.18	52	0.08	15% Ethanol at 99°C	0-2h	12	0.019
									2-4h	6	0.009
									4-6h	2	0.003
									0-6h	*20*	*0.03*
Sciessent IIIB 6.7.1.2-05	AJ10D	Coated steel (powder coat)	7	2.5	0.18	52	0.08	15% Ethanol at 99°C	0-2h	20	0.031
									2-4h	4	0.006
									4-6h	1	0.002
									0-6h	*25*	*0.04*
Sciessent IIIB 6.7.1.2-06	AK10D	Acrylic coating on oriented PP	10	4.9	0.49	52	0.15	15% Ethanol at 99°C	0-2h	510	1.48
									2-4h	520	1.51
									4-6h	250	0.73
									0-6h	*1280*	*3.72*
Sciessent IIIB 6.7.1.2-01	Silver Antimicrobial Type AK	LLDPE	10	4.9	0.49	48	0.075	Olive Oil at 40°C	0-2h	<10	<0.015
									2-4h	<10	<0.015
									4-6h	<10	<0.015
									0-6h	*30*	*0.05*
Sciessent IIIB 6.7.1.2-03		PBT	10	4.9	0.51	48	0.075	Olive Oil at 175°C	0-2h	13	0.020
									2-4h	12	0.019
									4-6h	<10	<0.015
									0-6h	*35*	*0.05*
Sciessent IIIB 6.7.1.2-02		PVC	10	4.9	0.48	48	0.075	Olive Oil at 75°C	0-2h	20	0.031
									2-4h	40	0.062
									4-6h	52	0.081
									0-6h	*112*	*0.17*
Sciessent IIIB 6.7.1.2-04		Polystyrene	9	4.9	0.44	48	0.075	Olive Oil at 175°C	0-6h	-	-
	AJ10D		7	2.5	0.18	52	0.08	Olive Oil at 175°C	0-2h	<10	<0.016

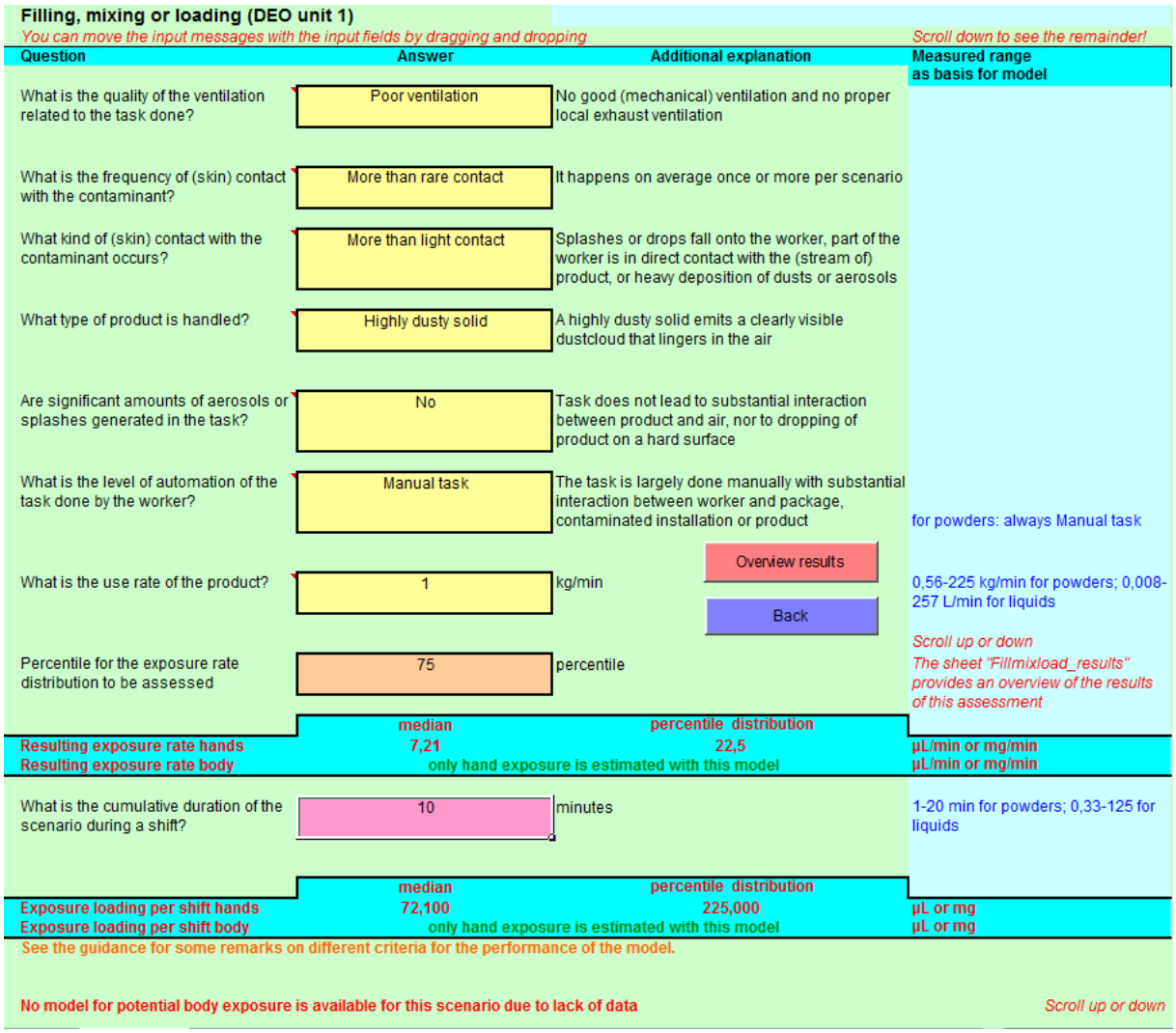
Test reference	Product type	Polymer type	Concentration of SZZ in polymer	Conc. of silver in SZZ	Conc. of silver in polymer	Surface area of test item	Volume of test medium	Test medium	Exposure time	Measured concentration of Ag in medium	Migration rate
			%	%	%	cm^2	L			µg*L-1	µg*cm-2
Sciessent IIIB 6.7.1.2-05		Coated steel (paint and powder coat)							2-4h	<10	<0.016
									4-6h	<10	<0.016
									0-6h	*30*	*0.05*
Sciessent IIIB 6.7.1.2-06	AK10D	Acrylic coating on oriented PP	10	4.9	0.49	52	0.15	Olive Oil at 125°C	0-2h	19	0.055
									2-4h	22	0.064
									4-6h	24	0.070
									0-6h	*65*	*0.19*

3 Human exposure calculations

INDUSTRIAL EXPOSURE

Scenario 1 - Mixing and loading (incl. transport, packaging and maintenance)

The RISKOFDERM model is used for dermal exposure and the MEASE model, specifically developed for metal compounds, is used for inhalation exposure, in line with the concept agreed for silver zinc zeolite.



Filling, mixing or loading (DEO unit 1)

You can move the input messages with the input fields by dragging and dropping — *Scroll down to see the remainder!*

Question	Answer	Additional explanation	Measured range as basis for model
What is the quality of the ventilation related to the task done?	Poor ventilation	No good (mechanical) ventilation and no proper local exhaust ventilation	
What is the frequency of (skin) contact with the contaminant?	More than rare contact	It happens on average once or more per scenario	
What kind of (skin) contact with the contaminant occurs?	More than light contact	Splashes or drops fall onto the worker, part of the worker is in direct contact with the (stream of) product, or heavy deposition of dusts or aerosols	
What type of product is handled?	Highly dusty solid	A highly dusty solid emits a clearly visible dustcloud that lingers in the air	
Are significant amounts of aerosols or splashes generated in the task?	No	Task does not lead to substantial interaction between product and air, nor to dropping of product on a hard surface	
What is the level of automation of the task done by the worker?	Manual task	The task is largely done manually with substantial interaction between worker and package, contaminated installation or product	for powders: always Manual task
What is the use rate of the product?	1	kg/min	0,56-225 kg/min for powders; 0,008-257 L/min for liquids
Percentile for the exposure rate distribution to be assessed	75	percentile	*Scroll up or down* *The sheet "Fillmixload_results" provides an overview of the results of this assessment*

Overview results | Back

	median	percentile distribution	
Resulting exposure rate hands	7,21	22,5	µL/min or mg/min
Resulting exposure rate body	only hand exposure is estimated with this model		µL/min or mg/min

What is the cumulative duration of the scenario during a shift?	10	minutes	1-20 min for powders; 0,33-125 for liquids

	median	percentile distribution	
Exposure loading per shift hands	72,100	225,000	µL or mg
Exposure loading per shift body	only hand exposure is estimated with this model		µL or mg

See the guidance for some remarks on different criteria for the performance of the model.

No model for potential body exposure is available for this scenario due to lack of data — *Scroll up or down*

MEASE input parameters and output values	
Substance characteristics	Model parameters
Molecular weight (g/mol)	Not relevant
Melting point (°C)	Not relevant
Vapour pressure (Pa)	Not relevant
Physical form	Solid, high dustiness

Content in preparation (including alloys)	>25%
Operational conditions (OC)	Model parameters
Process category	Mixing or blending in batch processes for formulation of preparation and articles
Process temperature (°C)	Not relevant
Scale of operation	Professional use
Duration of exposure (minutes)	<15 min
OCs used for dermal exposure assessment	Model parameters
Pattern of use	Wide dispersive use
Pattern of exposure control	Direct handling
Contact level	Extensive
Risk management measures (RMM)	Model parameters
Implemented RMMs	No RMM
RMM efficiency based on	Lower confidence limit
Respiratory protective equipment (RPE)	No RPE
Use of gloves	No gloves
Exposure estimate	
Dermal exposure estimate	50 µg/(cm² x d)
Exposed skin area	480 cm²
Total dermal loading	24 mg/d
Inhalation exposure estimate	5 mg/m³

Summary table: systemic exposure from industrial uses				
Exposure scenario	**Tier/PPE**	**Estimated inhalation uptake**	**Estimated dermal uptake**	**Estimated total uptake**
Scenario 1 mixing and loading	Tier 1	0.017 mg/kg bw per day	0.0094 mg/kg bw per day	0.026 mg/kg bw per day
	Tier 2 Respiratory protection (95%)	0.00085 mg/kg bw per day	0.0094 mg/kg bw per day	0.01025 mg/kg bw per day
	Tier 2 Respiratory protection (95%) and protective gloves (95%)	0.00085 mg/kg bw per day	0.00047mg/kg bw per day	0.0013 mg/kg bw per day

PROFESSIONAL EXPOSURE

Scenario 2 - Spray application (incl. cleaning of spraying equipment)

Spray application - standard model for antifouling paints and spraying (TNsG)			
Dermal			
Input			
	Indicative dermal exposure:		
	Hands without protective gloves	119	mg/min
	Hands inside gloves	2.04	mg/min
	Body	250	mg/min

	Exposure duration	180	min/d
	Concentration of product in coating	5	%
Output			
	Tier 1		
	Dermal deposit		
	Hands without protective gloves	1071	mg
	Body	2250	mg
	Total dermal deposit of product	**3321**	**mg/d**
	Tier 2		
	Hands inside gloves	18.4	mg
	Body protected with overall (95% protection)	112.5	mg
	Total dermal deposit of product	**131**	**mg/d**

Inhalation			
Input			
	Indicative inhalation exposure (non-volatile compounds):	17.3	mg/m^3
	Exposure duration	180	min/d
	Inhalation rate	1.25	m^3/h
	Concentration of product in coating	5	%
Output			
	Tier 1		
	Inhalation exposure estimate of product	**3.2**	**mg/d**
	Tier 2		
	Inhalation exposure estimate of product. 95% reduction due to use of respiratory protection	**0.16**	**mg/d**

Scenario 3.1 - Brush and roller application by professionals

Brush and roller application - consumer paint model 4, HEEG opinion 15			
Dermal			
Input			
	Indicative dermal exposure:		
	Hands without protective gloves	76.6	mg/min
	Hands inside gloves	18.5	mg/min
	Body, potential value	30.7	mg/min
	Body, 95% body exposure reduction using impermeable coverall	1.54	mg/min
	Exposure duration	90	min/d
	Concentration of product in coating	5	%
Output			
	Tier 1		
	Dermal deposit		

	Hands without protective gloves	345	mg
	Body, 95% body exposure reduction using impermeable coverall	138	mg
	Total dermal deposit of product	**483**	**mg/d**
	Tier 2		
	Hands inside gloves	83	mg
	Body, 95% body exposure reduction using impermeable coverall	6.9	mg
	Total dermal deposit of product	**90**	**mg/d**

Scenario 4 - Manual application of sealants

Tier 1 CONSEXPO model: Joint sealant	
Dermal model	Direct dermal contact with product: constant rate
active substance % (w/v)	5%
Duration and frequency of task	300 min during a work shift
Contact rate	50 mg/min
Output	
Dermal external dose	750 mg

Tier 2 migration rate: application of sealant		
Migration rate initial (silver ions)	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
Exposure duration	300 min	
Surface area	2 cm^2	CONSEXPO default for manual application of joint sealant (two finger tips)
Dermal external dose per work shift	1.31 µg silver ions	

NON-PROFESSIONAL EXPOSURE

Scenario 3.2 - Brush and roller application by non-professionals

CONSEXPO model: Brush and roller painting: high solid paint	
Dermal model	Direct dermal contact with product: constant rate
active substance % (w/v)	5%
Duration and frequency of task	120 min
Contact rate	30 mg/min
Output	
Dermal external dose	180 mg

SECONDARY EXPOSURE OF THE GENERAL PUBLIC EXCLUDING DIETARY EXPOSURE

Scenario 5 - Dermal exposure to treated polymer: direct contact with human skin

Calculations for Scenario *5.1* small scale

- Acute dermal exposure = MR initial x t x SA/BW
- Repeated dermal exposure = acute exposure

MR initial = initial release phase (0- 2h)
t = exposure duration
SA = hand surface area in contact with article
BW = body weight

Adult		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	60 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.0167 h	1 min; eCA assumption
Hand surface area	0.041 m^2	Biocides Human Health Exposure Methodology
Acute/repeated dermal exposure	0.014 µg * kg^{-1} * day^{-1}	

Child		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	23.9 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.0167 h/d	1 min; eCA assumption
Hand surface area	0.021 m^2	Biocides Human Health Exposure Methodology
Acute/repeated dermal exposure	0.020 µg * kg^{-1} * day^{-1}	

Toddler		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	10 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.0167 h	1 min; eCA assumption
Hand surface area	0.012 m^2	Biocides Human Health Exposure Methodology
Acute/repeated dermal exposure	0.025 µg * kg^{-1} * day^{-1}	

Infant		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	8 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.0167 h	1 min; eCA assumption
Hand surface area	0.010 m^2	Biocides Human Health Exposure Methodology

Acute/repeated dermal exposure	0.027 µg * kg^{-1} * day^{-1}	

Calculations for Scenario *5.2* medium scale

- Acute dermal exposure = MR initial x t x SA/BW
- Repeated dermal exposure = MR constant x t x SA/BW

MR initial = initial release phase (0- 2h)
MR constant = release rate after 8h and onward
t = exposure duration
SA = hand surface area in contact with article
BW = body weight

Adult		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	0.22 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	60 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.5 h	eCA assumption
Exposed surface area	300 cm^2	Biocides Human Health Exposure Methodology
Acute dermal exposure	0.33 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	0.019 µg * kg^{-1} * day^{-1}	

Child		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	0.22 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	23.9 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.5 h/d	eCA assumption
Exposed surface area	300 cm^2	Biocides Human Health Exposure Methodology
Acute dermal exposure	0.82 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	0.048 µg * kg^{-1} * day^{-1}	

Toddler		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	0.22 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	10 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.5 h	eCA assumption
Exposed surface area	200 cm^2	Biocides Human Health Exposure Methodology
Acute dermal exposure	1.31 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	0.072 µg * kg^{-1} * day^{-1}	

Infant		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	0.22 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	8 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.5 h	eCA assumption
Exposed surface area	200 cm^2	Biocides Human Health Exposure Methodology

Acute dermal exposure	1.64 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	0.096 µg * kg^{-1} * day^{-1}	

Calculations for Scenario *5.3* large scale

- Acute dermal exposure = [(MR initial * 2) + (MR intermediate * (t-2)] x SA/BW
- Repeated dermal exposure = MR constant * t * SA/BW

MR initial = initial release phase (0- 2h)
MR intermediate = geometric mean release (2h-8h)
MR constant = release rate after 8h and onward
t = exposure duration
SA = body surface area in contact with article
BW = body weight

Adult		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR intermediate	32 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	7.7 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	60 kg	Biocides Human Health Exposure Methodology
Exposure duration	3 h	eCA assumption
Exposed surface area	0.581 m^2	Biocides Human Health Exposure Methodology
Acute dermal exposure	28 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	2.24 µg * kg^{-1} * day^{-1}	

Child		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR intermediate	32 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	7.7 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	23.9 kg	Biocides Human Health Exposure Methodology
Exposure duration	3 h	eCA assumption
Exposed surface area	0.322 m^2	Biocides Human Health Exposure Methodology
Acute dermal exposure	40 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	3.1 µg * kg^{-1} * day^{-1}	

Toddler		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR intermediate	32 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	7.7 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	10 kg	Biocides Human Health Exposure Methodology
Exposure duration	3 h	eCA assumption
Exposed surface area	0.168 m^2	Biocides Human Health Exposure Methodology
Acute dermal exposure	49 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	3.9 µg * kg^{-1} * day^{-1}	

Infant		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR intermediate	32 ng * cm^{-2} x h^{-1}	See chapter 8.6

MR constant	7.7 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	8 kg	Biocides Human Health Exposure Methodology
Exposure duration	3 h	eCA assumption
Exposed surface area	0.144 m^2	Biocides Human Health Exposure Methodology
Acute dermal exposure	53 µg * kg^{-1} * day^{-1}	
Repeated dermal exposure	4.2 µg * kg^{-1} * day^{-1}	

Scenario 6 - Oral exposure to treated polymer: hand-to-mouth contact

Calculation:

- Acute dermal exposure = MR initial x SA x proportion x transfer coefficient/BW
- Repeated dermal exposure = MR constant x t x SA x proportion x transfer coefficient/BW

MR initial = initial release phase (0- 2h)
MR constant = release rate after 8h and onward
t = exposure duration
SA = hand surface area in contact with floor
proportion = Proportion of palms of hand in contact with floor = 0.4
transfer coefficient = Hand to mouth transfer coefficient = 0.5
BW = body weight

Toddler		
MR initial	131 ng * cm^{-2} x h^{-1}	Migration into artificial alkaline sweat. See chapter 8.6
MR constant	7.7 ng * cm^{-2} x h^{-1}	Migration into artificial alkaline sweat. See chapter 8.6
Body weight	10 kg	Biocides Human Health Exposure Methodology
Exposure duration	1 h	RIVM report no 612810012/2002 (chapter 2)
Hand surface area	115 cm^2	2 hand palms. Biocides Human Health Exposure Methodology
Proportion of palms of hand in contact with floor	0.4	Recommendation 5 of the BPC Ad hoc Working Group on Human Exposure, Non-professional use of antifouling paints
Hand to mouth transfer coefficient	0.5	
Acute oral exposure	**0.302 µg * kg^{-1} * day^{-1}**	
Repeated oral exposure	**0.018 [µg * kg^{-1} * day^{-1}**	

Infant		
MR initial	131 ng * cm^{-2} x h^{-1}	Migration into artificial alkaline sweat. See chapter 8.6
MR constant	7.7 ng * cm^{-2} x h^{-1}	Migration into artificial alkaline sweat. See chapter 8.6
Body weight	8 kg	Biocides Human Health Exposure Methodology
Exposure duration	1 h	RIVM report no 612810012/2002 (chapter 2)
Hand surface area	98 cm^2	2 hand palms. Biocides Human Health Exposure Methodology
Proportion of palms of hand in contact with floor	0.4	Recommendation 5 of the BPC Ad hoc Working Group on Human Exposure, Non-professional use of antifouling paints
Hand to mouth transfer coefficient	0.5	
Acute oral exposure	**0.321 µg * kg^{-1} * day^{-1}**	
Repeated oral exposure	**0.019 [µg * kg^{-1} * day^{-1}**	

Scenario 7 - Oral exposure to treated polymer: taking into mouth

Calculations for Scenario 7.1 small scale

- Acute dermal exposure = MR initial x t x SA/BW
- Repeated dermal exposure = MR constant x t x SA/BW

MR initial = initial release phase (0-2h)
MR constant = release rate after 8h and onward
t = exposure duration
SA = body surface area in contact with article
BW = body weight

Adult		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	7 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	60 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.08 h	5 min, eCA assumption
Exposed surface area	63 cm^2	eCA assumption
Acute oral exposure	0.011 µg * kg^{-1} * day^{-1}	
Repeated oral exposure	0.0006 µg * kg^{-1} * day^{-1}	

Child		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	7 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	23.9 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.08 h	5 min, eCA assumption
Exposed surface area	63 cm^2	eCA assumption
Acute oral exposure	0.029 µg * kg^{-1} * day^{-1}	
Repeated oral exposure	0.0008 µg * kg^{-1} * day^{-1}	

Toddler		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	7 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	10 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.08 h	5 min, eCA assumption
Exposed surface area	31 cm^2	eCA assumption
Acute oral exposure	0.034 µg * kg^{-1} * day^{-1}	
Repeated oral exposure	0.0018 µg * kg^{-1} * day^{-1}	

Calculations for Scenario 7.2 large-scale A) pacifier

- Acute dermal exposure = [(MR initial * 2) + (MR intermediate * (t-2)] x SA/BW
- Repeated dermal exposure = MR constant x t x SA/BW

MR initial = initial release phase (0-2h)
MR intermediate = geometric mean release (2h-8h)
MR constant = release rate after 8h and onward
t = exposure duration

SA = body surface area in contact with article
BW = body weight

Toddler		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	7 ng * cm^{-2} x h^{-1}	Biocides Human Health Exposure Methodology
Exposure duration	1.4 h	82 min per day acc to RIVM report no 612810012/2002 (chapter 2)
Exposed surface area	12.6 cm^2	eCA assumption
Acute oral exposure	0.54 µg * kg^{-1} * day^{-1}	
Repeated oral exposure	0.052 µg * kg^{-1} * day^{-1}	

Infant		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR intermediate	7 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	0.77 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	8 kg	Biocides Human Health Exposure Methodology
Exposure duration	4.75 h	285 min per day acc. to RIVM report no 612810012/2002 (chapter 2)
Exposed surface area	12.6 cm^2	eCA assumption
Acute oral exposure	0.31 µg * kg^{-1} * day^{-1}	
Repeated oral exposure	0.012 µg * kg^{-1} * day^{-1}	

Calculations for Scenario 7.2 large-scale, B) mouthguard

- Acute dermal exposure = [(MR initial * 2) + (MR intermediate * (t-2)] x SA/BW
- Repeated dermal exposure = MR constant x t x SA/BW

MR initial = initial release phase (0-2h)
MR intermediate = geometric mean release (2h-8h)
MR constant = release rate after 8h and onward
t = exposure duration
SA = body surface area in contact with article
BW = body weight

Adult		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR intermediate	7 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	0.22 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	60 kg	Biocides Human Health Exposure Methodology
Exposure duration	8 h	eCA assumption
Exposed surface area	20 cm^2	eCA assumption
Acute oral exposure	0.15 µg * kg^{-1} * day^{-1}	
Repeated oral exposure	0.019 µg * kg^{-1} * day^{-1}	

Child		
MR initial	131 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR intermediate	7 ng * cm^{-2} x h^{-1}	See chapter 8.6
MR constant	0.22 ng * cm^{-2} x h^{-1}	See chapter 8.6
Body weight	23.9 kg	Biocides Human Health Exposure Methodology

Exposure duration	8 h	eCA assumption
Exposed surface area	20 cm^2	eCA assumption
Acute oral exposure	0.37 µg * kg^{-1} * day^{-1}	
Repeated oral exposure	0.047 µg * kg^{-1} * day^{-1}	

Scenario 8 - Oral exposure to treated textile: taking into mouth

Estimating the weight of textile item: We assume that the mouthed textile object has the size of a sphere with a diameter of 2 cm (identical to pacifier scenario), making a volume of 4.2 cm^3. We assume that a piece of textile crumpled into such a sphere weighs 1.3 g. This assumption is based on a very simple test with 5 pieces of textile of different material and thickness. Each piece was cut to a size that fits loosely crumpled into a 10 mL cylinder. The cut piece was then weighed; and the average weight of the pieces was 3g, making a weight/volume ratio of 0.3 g/cm^3.

Repeated exposure is not different from acute exposure, based on the assumption that different parts of the textile item are mouthed each time.

Calculation:
- Acute oral exposure = MR initial x t x SA/BW
- Repeated oral exposure = acute oral exposure

Toddler		
MR initial	10.4 % * h^{-1}	See chapter 8.6
Ag content	0.025%	applicant
Weight of mouthed piece of textile	1.3 g	eCA assumption
Exposure duration	0.38 h	23 min per day acc to RIVM report no 612810012/2002 (chapter 2)*
Body weight	10 kg	Biocides Human Health Exposure Methodology
Acute/repeated oral exposure	**1.2 µg * kg^{-1} * d^{-1}**	

Infant		
MR initial	10.4 % * h^{-1}	See chapter 8.6
Ag content	0.025%	applicant
Weight of mouthed piece of textile	1.3 g	eCA assumption
Body weight	8 kg	Biocides Human Health Exposure Methodology
Exposure duration	0.13 h	8 min per day acc. to RIVM report no 612810012/2002 (chapter 2)*
Acute/repeated oral exposure	**0.53 µg * kg^{-1} * d^{-1}**	

* the chosen value is lower compared to the value chosen for silver zinc and silver copper zeolite, since no application in apparel is intended, i.e. the infant or toddler are not expected to suck on their or other cloths. Consequently, we chose default value for non-toys from the RIVM report.

Scenario 9 - Dermal exposure to treated textile: direct contact with human skin

Calculations for Scenario 9.2 – small-scale

Values used in calculations		
Ag concentration in textile	0.025%	
Ag released fraction - acute	33%	Applying the calculation initial release over 2h plus intermediate release over hours 2-8 would result in 36.4 %. Since this would be higher than the total release over the first 24h, the 24h-value is chosen. See chapter 8.6
Ag released fraction- repeated	4.1%	Exposure 8h per day. See chapter 8.6
Ag released - acute	15.0 mg * m^{-2}	
Ag released - repeated	1.8 mg * m^{-2}	
specific weight of the fabric	180g * m^{-2}	
contact time	8h	

Calculation:

- Dermal exposure = Ag concentration in textile * specific weight of textile * released fraction x SA/BW

SA = body surface area in contact with article
BW = body weight

Infant		
Body weight	8 kg	Biocides Human Health Exposure Methodology
Body surface area	0.017 m2	Biocides Human Health Exposure Methodology
Acute dermal exposure	**32.4 µg * kg^{-1} * d^{-1}**	
Repeated dermal exposure	**4.0 µg * kg^{-1} * d^{-1}**	

Toddler		
Body weight	10 kg	Biocides Human Health Exposure Methodology
Body surface area	0.020 m2	Biocides Human Health Exposure Methodology
Acute dermal exposure	**30.3 µg * kg^{-1} * d^{-1}**	
Repeated dermal exposure	**3.7 µg * kg^{-1} * d^{-1}**	

Child		
Body weight	23.9 kg	Biocides Human Health Exposure Methodology
Body surface area	0.042 m2	Biocides Human Health Exposure Methodology
Acute dermal exposure	**26.6 µg * kg^{-1} * d^{-1}**	
Repeated dermal exposure	**3.3 µg * kg^{-1} * d^{-1}**	

Adult		
Body weight	60 kg	Biocides Human Health Exposure Methodology
Body surface area	0.079 m2	Biocides Human Health Exposure Methodology
Acute dermal exposure	**19.8 µg * kg^{-1} * d^{-1}**	
Repeated dermal exposure	**2.4 µg * kg^{-1} * d^{-1}**	

Calculations for Scenario 9.3 – textile handling

- Dermal exposure = Ag concentration in textile * specific weight of textile * released fraction x SA/BW

SA = hand surface area in contact with article
BW = body weight

Toddler		
Ag released fraction - acute	22.1%	Exposure during 2h. See chapter 8.6
Ag content	0.025%	applicant
Body weight	10 kg	Biocides Human Health Exposure Methodology
Body surface area	0.012 m^2	
Acute/repeated dermal exposure	**11.5 µg * kg^{-1} * d^{-1}**	

Child		
Ag released fraction - acute	22.1%	Exposure during 2h. See chapter 8.6
Ag content	0.025%	applicant
Body weight	23.9 kg	Biocides Human Health Exposure Methodology
Body surface area	0.021 m^2	
Acute/repeated dermal exposure	**8.9 µg * kg^{-1} * d^{-1}**	

Adult		
Ag released fraction - acute	22.1%	Exposure during 2h. See chapter 8.6
Ag content	0.025%	applicant
Body weight	60 kg	Biocides Human Health Exposure Methodology
Body surface area	0.041 m^2	
Acute/repeated dermal exposure	**6.8 µg * kg^{-1} * d^{-1}**	

DIETARY EXPOSURE

Scenario D1 – Food contact materials

Calculations for Scenario D1

The polymer surface may be a treated article, for example a cutting board, or a coated surface, for example a kitchen top. Potential dietary intake of silver resulting from the use of the biocidal product in various polymers can be calculated using the maximum value observed in migration studies in food simulants as a conservative estimate of potential dietary exposure. The applicant did not provide migration studies specifically with silver zeolite, but with silver zinc zeolite. The applicant provided data on migration from different polymer types treated with silver zinc zeolite into food simulants (3% acetic acid at 5°C and 40°C, 15% ethanol at 40°C or 99°C and olive oil at various temperatures), which are listed in chapter 2.c of annex II. The migration of silver from such materials is strongly influenced by polymer type, food contact media and contact time. Silver migration is correlated to the ionic strength of the medium. Therefore, acetic acid is chosen as the worst-case food simulant for this kind of compounds, releasing silver via ion exchange. When considering all available migration data with zeolites (See Apepndix II 2.a) the difference between SZ and SZZ appears to be 3-5 times (more released from SZ than SZZ). The

loading rate in the migration test is 2x higher than the final concentration claimed by the applicant. Therefore a safety factor 2 seems appropriate. Therefore, we use the migration study with silver zinc zeolite zeolite together with a safety factor of 2 in order to estimate migration rates used in this evaluation.

The estimate is based on the assumption that 1 kg of food coming into contact with 6 dm^2 of food contact material is consumed per day. This assumption is taken from Regulation (EU) No 10/2011 and Note for Guidance for Food Contact Materials by EFSA (Updated on 30/07/2008). Using the available migration data implicitly contains the assumption that the contact duration with food is 2h. The highest and lowest migration rates among the polymers tested (PVC and paint coated steel, respectively) are used in further exposure assessment.

Migration of silver from polymers into food simulants

Test reference	Product type	Polymer type	Conc. of product in polymer	Conc. of silver in SCAS	Conc. of silver in polymer	Test medium	Migration rate 0-2h	Safety factor	Extrapolated migration rate 0 – 2h
			%	%	%		µg * cm^{-2}		µg * cm^{-2}
Sciessent IIIB 6.7.1.2-01	Silver zinc zeolite Antimicrobial Type AK	LLDPE	10	4.9	0.49	3% acetic acid at 40°C	0.89	2	1.8
Sciessent IIIB 6.7.1.2-03		PBT	10	4.9	0.51	3% acetic acid at 99°C	0.27	2	0.5
Sciessent IIIB 6.7.1.2-02		PVC	10	4.9	0.48	3% acetic acid at 99°C	2.06	2	4.1
Sciessent IIIB 6.7.1.2-04		Polystyrene	9.02	4.9	0.44	3% acetic acid at 99°C	1.10	2	2.2
Sciessent IIIB 6.7.1.2-05	Silver zinc zeolite AJ10D	Coated steel (paint coat)	7	2.5	0.18	3% acetic acid at 99°C	0.13	2	0.27
Sciessent IIIB 6.7.1.2-06	Silver zinc zeolite AK10D	Acrylic coating on oriented PP	10	4.9	0.49	3% acetic acid at 99°C	1.95	2	3.9

Calculation:

- Acute oral exposure days = maximum release x contact surface area x daily food intake/BW
- Repeated oral exposure = Acute oral exposure

BW = body weight

Infant				
Ag release rate	PVC Coated steel (paint coat)	4.1 0.27	µg * cm^{-2} µg * cm^{-2}	
Daily food intake	1 kg			Note for Guidance for Food Contact Materials European Food Safety Authority; Updated on 30/07/2008
Contact surface area	6 dm^2			Regulation (EU) No 10/2011
Body weight	8 kg			Biocides Human Health Exposure Methodology
Acute/repeated oral exposure	**PVC** **Coated steel (paint coat)**	**309** **20**	**µg * kg^{-1} * d^{-1}** **µg * kg^{-1} * d^{-1}**	

Toddler				
Ag release rate	PVC Coated steel (paint coat)	4.1 0.27	µg * cm^{-2} µg * cm^{-2}	
Daily food intake	1 kg			Note for Guidance for Food Contact Materials European Food Safety Authority; Updated on 30/07/2008
Contact surface area	6 dm^2			Regulation (EU) No 10/2011
Body weight	10 kg			Biocides Human Health Exposure Methodology
Acute/repeated oral exposure	**PVC** **Coated steel (paint coat)**	**247** **16**	**µg * kg^{-1} * d^{-1}** **µg * kg^{-1} * d^{-1}**	

Child				
Ag release rate	PVC Coated steel (paint coat)	4.1 0.27	µg * cm^{-2} µg * cm^{-2}	
Daily food intake	1 kg			Note for Guidance for Food Contact Materials European Food Safety Authority; Updated on 30/07/2008
Contact surface area	6 dm^2			Regulation (EU) No 10/2011
Body weight	23.9 kg			Biocides Human Health Exposure Methodology
Acute/repeated oral exposure	**PVC** **Coated steel (paint coat)**	**103** **6.8**	**µg * kg^{-1} * d^{-1}** **µg * kg^{-1} * d^{-1}**	

Adult				
Ag release rate	PVC Coated steel (paint coat)	4.1 0.27	µg * cm^{-2} µg * cm^{-2}	
Daily food intake	1 kg			Note for Guidance for Food Contact Materials European Food Safety Authority; Updated on 30/07/2008
Contact surface area	6 dm^2			Regulation (EU) No 10/2011
Body weight	60 kg			Biocides Human Health Exposure Methodology
Acute/repeated oral exposure	**PVC** **Coated steel (paint coat)**	**41** **2.7**	**µg * kg^{-1} * d^{-1}** **µg * kg^{-1} * d^{-1}**	

Scenario D2 – Preservation of water filter

Calculations for Scenario D2

Remark: The scenario has previously been presented in the CAR for silver zinc zeolite. No information specific for silver zeolite has been provided by the applicant. Here, only the default values have been adjusted to the Biocides Human Health Exposure Methodology (ECHA 2015). The scenario for repeated exposure has been removed, since the water filter are applied in flow-through systems. The default values for water consumption might need to be updated.

The estimate is based on the assumption that a person consumes a certain amount of water per day for drinking or food preparation, according EPA exposure factors handbook (chapter 3). The water has passed through an activated carbon filter. The filter material contains silver zeolite. Leaching test shows that silver is release at a maximum of ca 22 µg/L and a mean of ca 20 µg/L through the first 3400L of passing water, according to study IIIB 5.10.2-11.

Calculation:

- Acute oral exposure = maximum release x daily water consumption/BW

BW = body weight

Exposure scenarios

Infant		
Body weight	8 kg	Biocides Human Health Exposure Methodology
Daily intake of water	0.55 L/d	EPA exposure factors handbook, chapter 3 (2011)
Acute oral exposure	1.5 µgAg/(kg x d)	

Toddler		
Body weight	10 kg	Biocides Human Health Exposure Methodology
Daily intake of water	0.31 L/d	EPA exposure factors handbook, chapter 3 (2011)
Acute oral exposure	0.68 µgAg/(kg x d)	

Child		
Body weight	23.9 kg	Biocides Human Health Exposure Methodology
Daily intake of water	0.48 L/d	EPA exposure factors handbook, chapter 3 (2011)
Acute oral exposure	0.44 µgAg/(kg x d)	

Adults		
Body weight	60 kg	Biocides Human Health Exposure Methodology
Daily intake of water	1 L/d	EPA exposure factors handbook, chapter 3 (2011)
Acute oral exposure	0.37 µgAg/(kg x d)	

Appendix III: Environmental emission (and exposure) calculations

EMISSION ESTIMATION

Scenario 2.1 – Wall and floor covering

We use the default surface area cleaned in industrial and institutional areas (1000 m^2, ESD PT2) in order to estimate the release of silver during cleaning. We assume that silver is released at the rate determined in the migration test with distilled water (details in introduction to chapter 9). We further assume that the room is cleaned once per day every day, and hat the cleaning water has contact with the flooring for a duration of 30 minutes.

Input parameters for calculating the local emission - silver					
Parameter/variable		**Unit**	**Origin**	**Value**	
Scenario: modified PT2, cleaning of floor in industrial and institutional area					
Surface area to be disinfected	$AREA_{surface}$	m^2	D	1000	ESD PT2 default for industrial premises
Leaching rate		$\mu g * cm^{-2} * d^{-1}$	S	0,0019	IIIB 6.6-01 BASF (Ciba) in dossier fro silver zinc zeolite, details in introduction to chapter 9.
Number of applications per day	Nappl	d^{-1}	D	1	
Duration of task		h	D	0.5	eCA assumption, no guidance available
Fraction of substance disintegrated during or after application (before release to the sewer system)	F_{dis}	-	S	0	Silver does not disintegrate
Fraction released to wastewater	F_{water}	-	D	1	
Output					
Local release to waste water (without pretreatment)	$Elocal_{water}$	$kg * d^{-1}$	O	3.96E-07	$Elocal_{water}$ = AREAsurface * Nappl *(1 - Fdis) * Fwater * leaching rate * duration of task

Scenario 4.1 - Polymer formulation

For the release during polymer production. EUSES version 2.1.2 was used for the simulations.
The assessments were conducted for the life-cycle phase industrial use. The calculations were based on the tonnage of silver going into polymer consumer articles. The physical and chemical model input parameters are based on silver.

Assessment type model inputs for polymer production	
Assessment of biocides on local scale only	Yes
Environmental	Yes
Local scale	Yes
Run mode	Interactive

Defaults	Add defaults
Other options	Not selected

For the product types where polymer incorporation is relevant. the manufacture of the treated polymer and the production of the end-use items will take place in the same basic manner. even if treated articles for other PTs are manufactured: The first part of the process involves the addition of the active substance to a plastic 'masterbatch' which may involve a range of different polymers depending on the final intended use. The 'masterbatch' is then used by a molding company or fiber manufacturer to make end-use plastic items or man-made fibers. The process involves standard injection molding equipment or fiber spinning equipment which will be engineered to produce the intended items.

Within the EUSES model the handling. compounding and conversion of plastics is described under 'industrial use' for PT7 biocide scenarios, but it is equally applicable to polymers assessed for PT 4. Tonnage is entered into the model as the total amount of silver available from the silver additive.

The Guidance Volume IV Part B Annex 7 describes emissions for different use categories. Under Point 4 it is stated that "In case a substance is applied in a formulation at a rather low level, unrealistic values for the fraction of the main source and the number of days will be derived from the tables using the tonnage as such. Therefore a correction should be made; a suggestion is to correct the tonnage as input for the B-table in the following way. A similar suggestion is provided in the EUSES background report which states that "…the regional tonnage, TONNAGEreg, should be corrected for the estimation of the fraction of the main source and the number of emission days by the concentration or fraction of the substance in the polymer (Fpolymer)".

According to the applicant. the incorporation rate is the incorporation rate is 5% active substance and this value can be used to derive a revised $F_{mainsource}$ and emission period according to the above mentioned guideline. Using the total regional tonnage of substance of of *[confidential]* tonnes the polymer volume will be *[confidential]* tonnes per year and the corresponding $F_{mainsource}$ will be *[confidential]*. using Table B3.9 in the Volume IV Part B. According to the same table the emission period would be calculated to *[confidential]* days.

Default release fractions for handling, compounding and conversion are based on the entire active substance and do not consider that only a fraction of the silver is released. To account for this, an additional fraction of 1% is applied to the handling and compounding of the model (i.e. the default release fractions of the EUSES model are divided by 100). For conversion, a process which can be described as form-setting of the plastic, the masterbatch with the silver additive is already compounded into the plastic, so that release factors derived from migration of silver from the polymer can be taken into account. The highest migration rate derived in a test with buffer solutions (BASF III B 6.6-01) was 0.003 % per day (including correction factor 100, see introduction to chapter 9), which is used as fraction released to water during conversion.

Release estimation parameters for production of treated polymers		
Parameter	**Value**	**Type**
General input		
Scenario choice for biocides	(9) Fibre. leather. paper preservatives	S
Additional scenario information use	(9.3) Polymerised materials	S

Fraction of particles < 40 µm	100%. to maximise release to water as a worst-case	S
Fraction of particles > 40 µm	0%	S
Degree of closure during conversion	Closed	S
Volatility during compounding	Low	S
Fraction of silver in the polymer	0.25%	S
Tonnage of silver in EU	[confidential]	S
Regional tonnage of silver	[confidential]	O
Amount of plastic produced with the sub-stance. regional	[confidential]	O
Handling		
Is water used for cleaning operation	Yes. worst-case for environmental release	D
Fraction released to air	0	O
Fraction released to water <40 µm particles	0.006%	D
Fraction released to water >40 µm particles	0.002%	D
Fraction released to water during handling	0.006%	O
Compounding		
Is water used for cleaning operation	Yes	D
Fraction released related to volatility air	0	O
Fraction released to air	0	O
Fraction released to water <40 µm particles	0.0005%	S
Fraction released to water >40 µm particles	0.0001%	S
Fraction released to water during compound-ing	0.0005%	S
Conversion		
Organic or inorganic substance	Inorganic	S
Conversion process	Grinding/machining	D
Type of product formed	Foamed	D
Fraction released during conversion. related to volatility	0.002%	O
Fraction released to air during conversion	0	O
Fraction released to water during conversion	0.003%	S
Emission		
Fraction of tonnage released to air	0	O
Fraction of tonnage released to wastewater	[confidential]	O
Fraction of main local source	[confidential]	S
Number of emission days per year	[confidential]	S
Fraction of EU production volume for region	10 %	D

Output		
Local emission to air during episode (Elocal_air)	0 kg * d^{-1}	O
Local emission to wastewater during episode (Elocal_water)	[confidential]	O

Scenario 4.2 - Treated articles – service life – regional

Since no further information is available about distribution of the tonnage among exposure categories, the exposure category "wet " applies to the whole tonnage. This includes also

the use in water filters. Therefore, all further details are the same as for PT 9 and found in the emission estimation for PT 9 (scenario 9.4). Here, only those aspects are shown that differ between the product types.

Release to sewage water				
		Tonnage	RF * service life	Release
		[t/y]	%	[t/y]
Qwet	Tonnage silver going into "wet" applications	[confidential]	7.3	[confidential]

Scenario 7.1 - Polymers used on infrastructure

Application phase

Input parameters for calculating the local emission - silver					
Parameter/variable		**Unit**	**Origin**	**Value**	
City scenario:				sealants (bathroom)	
Fraction of silver in dry product	$F_{formdry}$		S	0.0025	applicant
Fraction of water in wet paint			D	0.15	CONSEXPO default for water content of high solid paints
Fraction of active substance in wet product	$F_{form-wet}$		O	0.0022	corrected by CONSEXPO default for water content
Volume of the product applied	V_{form}	L * m^{-2}	D	5.88	ESD City scenario, paints
Density of product	$RHO_{product}$	kg * m^{-3}	D	1000	ESD City scenario, paints
Fraction of product lost during application	F_{brush}		D	0.05	ESD City scenario, amateurs
			D	0.03	ESD City scenario, professionals
Number of houses treated per day	$N_{house, appl}$		D	1	ESD City scenario, paints
Treated surface area per house	AREA	m²	D	0.12	ESD City scenario, paints
Daily emission to wastewater	$E_{local water}$	kg * d^{-1}	O	7.67E-05	amateurs
			O	4.60E-05	professionals

Service life

Input parameters for calculating the local emission - silver					
Parameter/variable		**Unit**	**Origin**	**Value**	
City scenario				sealants (bath-room)	
Number of houses in a city	N_{house}		D	4000	
fraction of the houses on which paints are applied	f_{house}		D	1	
Number of houses that are contributing by leaching	$N_{house, leach}$		O	4000	
Service life	$T_{servicelife}$	years	D	10	
Area of the treated surface	AREA	m^2	D	0.12	
Tier 1: 100% leaching assumed					
Density of formulation	RHO_{form}	kg * m^{-3}	D	1000	
Volume applied	V_{form}	L * m^{-2}	D	5.88	
Fraction of active substance in dry product	$F_{formdry}$		S	0.0025	applicant
Fraction of water in wet paint			D	0.15	CONSEXPO default for water content of high solid paints
Fraction of active substance in wet product	$F_{formwet}$		O	0.0022	corrected by CONSEXPO default for water content
Cumulative leaching (100%) over assessment period	Q_{leach}	kg	O	0.0015	
daily emission to wastewater	**$Eloc al_{water}$**	**kg * d^{-1}**	**O**	**0.0017**	
Tier 2: laboratory leaching test					
Leaching rate, time 1		µg * cm^{-2} * d^{-1}	**S**	0.0019	
Leaching rate, time 2 and 3		µg * cm^{-2} * d^{-1}	**S**	0.00019	See chapter on migration in introduction to chapter 9
Time1 = time initial	T1 = $T_{initial}$	d	O	30	
Time2	T2	d	D	365	
Time3	T3	d	D	3650	
time for the longer assessment period 2	$T_{longer2}$	d		335	
time for the longer assessment period 3	$T_{longer3}$	d		3255	
number of houses in a city recently treated	$N_{house,initial}$			66	
number of houses in a city treated more than 30 days ago at tim2	$N_{house,longer,time2}$			367	

number of houses in a city treated more than 30 days ago at tim3	$N_{house,longer,time3}$			3567	
Cumulative leaching over time1	$Q_{leach,time1}$	mg * m^{-2}		0.571	There is a mismatch between Qleach for worst case and Qleach based on leaching test. In the first case, treated surface area area is included in Qleach.
Cumulative leaching over time2	$Q_{leach,time2}$	mg * m^{-2}		0.637	
Cumulative leaching over time3	$Q_{leach,time3}$	mg * m^{-2}		6.19	
daily emission to wastewater at time1	**$Elocal_{water,time1}$**	**mg * d^{-1}**	**O**	**0.15**	
daily emission to wastewater at time2	**$Elocal_{water,time2}$**	**mg * d^{-1}**	**O**	**0.65**	
daily emission to wastewater at time3	**$Elocal_{water,time3}$**	**mg * d^{-1}**	**O**	**2.2**	

Scenario 7.3 - Treated articles – service life – regional

The concept described in scenario 9.4 is here used for exposure assessment of migration for silver from treated polymer articles for PT7 as well. Since no further information is available about distribution of the tonnage among exposure categories, the exposure category "wet " applies to the whole tonnage. Therefore, all further details are the same as for PT 9 and found in the emission estimation for PT 9 (scenario 9.4). Here, only those aspects are shown that differ between the product types.

Release to sewage water				
		Tonnage	RF * service life	Release
		[t/y]	%	[t/y]
Qwet	Tonnage silver going into "wet" applications	[confidential]	7.3	[confidential]

Scenario 9.4 - Treated articles (including textiles) – service life – regional

Note: The general concept of exposure assessment has been agreed upon at the TM IV 2013 when the CAR for silver zinc zeolite was discussed. The agreed concept regards the exposure categories. release default values. distribution in the environment and the EUSES input parameters. The Working group asked the eCA to conduct separate exposure assessments for silver-containing substances and product type. However. the working group also recognized that aggregated exposure assessment has to be done. The aggregated exposure assessment for silver-containing active substances is presented in a separate document

Silver zeolite is one of a number of silver-containing active substances that are used to provide antimicrobial properties or functions to treated articles. Environmental exposure from treated articles is diffuse due to the variety of articles which can be treated with silver (and other ions where it applies). and due to the diversity of uses. This variety of uses

causes a great variety of exposure situations. However. to be able to make a realistic exposure assessment. it was necessary to summarize and to simplify exposure situations. Therefore. we generally used the tonnage approach for all exposure situations which are diffuse. This approach is supported by REACH guidance (R.17 "Estimation of Exposure from Articles"). It says:
"To calculate exposure for the environment. the estimated loading of the environment is calculated from release rates and the tonnage of the substance contained in the articles. Subsequently. the calculated or measured overall emission is treated as any other environmental emission in the current exposure estimation. The emissions during service life are considered to be diffuse emissions that usually cause exposure on a "regional" scale. …"
For this exposure assessment. the life cycle stages polymer production. service life and waste are taken into account. We do not distinguish between consumer use (usually used for liquid consumer products) and service life (usually used for articles) as this is not a meaningful category for this exposure assessment. We define both belonging to the life cycle stage service life. (See also definitions in chapter 5.1.2).

Exposure categories

Within the group polymer/coating applications, the use pattern during service life has a great effect on emission. We distinguished between "wipe uses" which get touched and wiped only occasionally (e.g. toilet seats, door handles, counter tops, kitchen wear, etc.) and "wet uses" which have frequent or constant water contact (drink containers, shower curtains, sewage pipes, sponges, etc.). We did not distinguish any further between polymers and coatings, because that has no directed effect on emissions from an end user product. Emissions both from polymers and from coatings can vary greatly (see introduction to chapter 9). A third group we distinguished are silver treated textiles as these have a different exposure pattern due to washing and wearing.

Wipe

The applicant did not specify the fraction of tonnage that is used in this category. Therefore. we assume that the whole tonnage might go into "wipe" applications". Migration rates for these use conditions could not be derived from the submitted migration tests, as they do not reflect an intermittent water contact (see introduction to chapter 9). That's why we based the migration rate for the "wipe" applications on the OECD ESD No. 3. "Emission scenario document on Plastic Additives" (OECD 2009). There, for biocides during service life, a migration rate of 0.01% per year to water is proposed for inorganic substances:

Wet

The applicant did not specify the fraction of tonnage that is used in this category. Therefore, we assume that the whole tonnage might go into "wet" applications". For these "wet" uses, we have applied the migration rate in migration tests submitted: 0.06
% loss in 15 days, which can be recalculated to 0.004%/day resp. 1.46%/year We assumed this migration rate yet to apply for the whole service life of the article.

Textiles

According to the applicant, silver zeolite is used in textiles but the textiles are not used for apparel. In this respect it is considered unlikely that textile articles will be washed regularly and release to drain can be considered to be similar to "wet " applications (see chapter 9.1.11.2).

eCA remark: it is currently not entirely clear whether the exclusion of use in apparel also covers bed textiles, or whether use in bed textiles is intended. We have asked the applicant for further clarification. Depending on their answer, we might need to adapt the exposure assessment. If bed textiles are included in the use, the tonnage has to be allocated to the exposure category "textile". However, this will not change the conclusions of the risk assessment.

Service life

The OECD Emission scenario document No. 3 also lists different service life times for different types of plastic materials, which reach from 0 to 20 years, depending on the application.

As silver treated articles are used for a broad range of applications, we have decided to generally apply 5 years of service life for "wet" and "wipe" articles.

The duration of service life has great influence on the amount of emissions. Only when a steady state is reached in society, i.e. the annual quantity removed by waste incineration, deposition, export of used articles, etc. is just as high as the quantity added annually, emissions can be calculated correctly. If a service life of 5 years is assumed, the amount of silver produced every year going into articles adds to the amount of silver already in society. Consequently, the accumulation time in society until a steady state is reached corresponds to the service life time. This means that emissions from articles with a service life > 1 year have to be multiplied with service life time to reflect the residence time of the article in society.

Assumptions made for migration rates and service life		
Type of use	Migration rate/loss assumed (Release Factor)	Service life/ accumulation in society
"Wipe"	0.01%/year	5 years
"Wet"	1.46%/year	5 years

As emissions from treated articles are wide dispersive, a regional scenario has to be taken into account. The regional release is calculated according to the equation:

$Eregional_{env} = Q_{consumer\ articles} / 10 \times RF_{env}$

The identified releases then have to be entered into a model to predict local environmental releases. For treated articles during service life, only the water path is relevant, as metals are not volatile. Direct contact with soil is also negligible. Consequently, only emissions to water are calculated.

The release of silver can be calculated as follows:

Release=(Qwet x RFwet x service life)+(Qwipe x RFwipe x service lfe)+ (Qtextiles total)

Distribution of tonnage silver to different applications and release to sewage water				
		Tonnage	RF * service life	Release
		[t/y]	%	[t/y]

Qwipe	Tonnage silver going into "wipe" applications	[confidential]	0.05	[confidential]
Qwet	Tonnage silver going into "wet" applications	[confidential]	7.3	[confidential]
				[confidential]*
* the tonnages were not added, since for all categories the whole tonnage was used as input value.				

The textile use resulted in the highest tonnage released to sewage. This tonnage was used as input value for the EUSES calculations.

Release from treated articles during waste stage

The calculations previously carried out for silver zinc zeolite showed that the contribution of waste disposal or waste incineration is negligible compared to the emission from polymer formulation and use of treated articles. The conditions are very similar for the actual active substance. Therefore, a further quantitative assessment for the waste stage is currently not necessary.
Under other circumstances, in case there are no emissions expected from polymer formulation (if it is not carried out in EU) or treated articles (no contact with water), an assessment of the waste stage might become necessary.

Release estimation

The release estimation is based on the tonnage of silver being released from consumer articles as described above.

Release estimation parameters for wide dispersive use		
Parameter	Value	Type
Scenario choice for biocides	(1) Human hygiene	S
Additional scenario information use	Not necessary	S
Tonnage of substance in Europe (= Emissions to water)	[confidential] t	S
Fraction of volume for region	10 %	D
Regional tonnage of substance ("private use" step)	[confidential] t	O
Emission days per year	365 days	D
Fraction of the local main source	0.002	D
Fraction released to wastewater	100%	D

EUSES model	

Usage	Wide dispersive use
IndCat	15/0 Others
UseCat	39 Biocides. non-agricultural
Life cycle step	Private use

Average percentage connection rate to STPs	90%

Appendix IV: List of terms and abbreviations

The abbreviations listed in the following were used in addition to standard terms and abbreviations as described in the Guidance documents for the Biocidal Products Regulation, for example in

https://echa.europa.eu/documents/10162/23036412/biocides_guidance_human_health_ra_iii_part_bc_en.pdf/30d53d7d-9723-7db4-357a-ca68739f5094

or

https://echa.europa.eu/documents/10162/23036412/bpr_guidance_ra_vol_iv_part_b_en.pdf/e2622aea-0b93-493f-85a3-f9cb42be16ae

Abbreviation	Explanation
ESD	Emission scenario document (https://echa.europa.eu/sv/guidance-documents/guidance-on-biocides-legislation/emission-scenario-documents)
SCAS	Silver-containing active substance
SCZ	Silver copper zeolite
SSHZP	Silver sodium hydrogen zirconium phosphate
SZ	Silver zeolite
SZZ	Silver zinc zeolite

Appendix V: Overall reference list *(including data owner and confidentiality claim)*

Reference list of IIIA studies submitted (by Section No.; please note: the numbers refer to the sections of the BPD, Annex II)

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
Section 1					
No references submitted.					
Section 2					
See the Confidential Annex					
Section 3					
IIIA 3.1.1-01 3.1.2-01 3.1.3-01 3.7-01	Cunningham, M.L.	2001	Physical/Chemical Characteristics of Zeomic AC10D. PTRL West Inc, Hercules, CA, USA. Project No. 1088W. GLP, Unpublished.	Yes	Sciessent
IIIA 3.1.1-02 3.1.2-02 3.1.3-02 3.3.1-01 3.3.2-01 3.3.3-01	Shepler, K.	2001	Physical/Chemical Characteristics of Zeomic AJ10D. PTRL-West Report No. 1001W-001. Submitted to US EPA, 25 pages. GLP, Unpublished.	Yes	Sciessent
IIIA 3.5-01	Bussey, R.J.	2001	Determination of the Solubility of Zeomic in Aqueous Solution. The National Food Laboratory Inc, Dublin, CA, USA. Project No. CA1119. GLP, Unpublished.	Yes	Sciessent
IIIA 3.11-01	Rivas, V. W.	2018	Silver Zeolite: Determination of the Relative Self-Ignition Temperature (Method 33.3.1.6 "Test N.4: Test method for self-heating substances", United Nations Publication 2009) IBACON GmbH, Rossdorf, Germany Study No. 131251188 GLP, Unpublished.	Y	Sciessent
Section 4					
IIIA 4.1 See the Confidential Annex					
Section 5					
IIIA 5.3.1-01	Simonetti, N., Simonetti, G., Bougnol, F., Scalzo, M.	1992	Electrochemical Ag+ for Preservative Use. Applied and Environmental Microbiology, Vol. 58, No. 12, p. 3834-3836. Non-GLP, Published.	No	--

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA 5.3.1-02	Inoue, Y., Hoshino, M., Takahashi, H., Noguchi, T., Murata, T., Kanzaki, Y., Hamashima, H. and Sasatsu, M.	2002	Bactericidal Activity of Ag-Zeolite Mediated by Reactive Oxygen Species Under Aerated Conditions, Journal of Inorganic Biochemistry, 92, p 37-42. Non-GLP, Published.	No	--
IIIA 5.3.1-03	Mavilia, L., Lo Curto, R.B., Postorino, G., Primerano, P. and Corigliano, F.	1999	Anti-microbic Activity and Action Mechanism of Silver (I) Exchanged Zeolites, Annali di Chimica, 89, p.341-350 Non-GLP, Published.	No	--
IIIA 5.3.1-04	Lin, Y-S.E., Vidic, R.D., Stout, J.E. and Yu, V.L.	1996	Individual and Combined Effects of Copper and Silver Ions on Inactivation of *Legionella pneumophila*. Wat. Res. Vol. 30, No.8. pp. 1905-1913. Non-GLP, Published.	No	--
IIIA 5.3.1-05	Yamanaka M, Hara K, Kudo J.	2005	Bactericidal actions of a silver ion solution on Escherichia coli, studied by energy-filtering transmission electron microscopy and proteomic analysis. Appl Environ Microbiol. 2005 Nov;71(11):7589-93. Non-GLP, Published.	No	--
IIIA 5.3.1-06	Choi O, Hu Z.	2008	Size dependent and reactive oxygen species related nanosilver toxicity to nitrifying bacteria. Environ Sci Technol. 2008 Jun 15;42(12):4583-8. Non-GLP, Published.	N	--
IIIA 5.3.1-07	Silvestry-Rodriguez N, Bright KR, Slack DC, Uhlmann DR, Gerba CP.	2008	Silver as a residual disinfectant to prevent biofilm formation in water distribution systems. Appl Environ Microbiol. 2008 Mar;74(5):1639-41. Non-GLP, Published.	N	--
IIIA 5.3.1-08	Pal S, Tak YK, Song JM.	2007	Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium Escherichia coli. Appl Environ Microbiol. 2007 Mar;73(6):1712-20. Non-GLP, Published.	N	--
IIIA 5.3.1-09	Chang Q, He H, Zhao J, Yang M, Qut J.	2008	Bactericidal activity of a Ce-promoted Ag/AlPO4 catalyst using molecular oxygen in water. Environ Sci Technol. 2008 Mar 1;42(5):1699-704. Non-GLP, Published.	N	--
IIIA 5.3.1-10	Kreth J, Kim D, Nguyen M, Hsiao G, Mito R, Kang MK, Chugal N, Shi W.	2008	The Antimicrobial Effect of Silver Ion Impregnation into Endodontic Sealer against Streptococcus mutans. Open Dent J. 2008;2:18-23. Non-GLP, Published.	N	--

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA 5.3.1-11	Pedahzur R, Katzenelson D, Barnea N, Lev O, Shuval HI, Fattal B, Ulitzur S.	2000	The efficacy of long-lasting residual drinking water disinfectants based on hydrogen peroxide and silver. Water Science & Technology 2000 Vol 42 No 1-2: 293–298. Non-GLP, Published.	N	--
IIIA 5.4.1-01	Matsumura, Y., Yoshikata, K., Kunisaki, S. and Tsuchido, T.	2003	Mode of Bactericidal Action of Silver Zeolite and Its Comparison with that of Silver Nitrate. Applied and Environmental Microbiology, Vol 69, No.7, p. 4278-4281. Non-GLP, Published.	N	--
IIIA 5.4.1-02	Thurman, R.B. and Gerba, C.P.	1989	The Molecular Mechanisms of Copper and Silver Ion Disinfection of Bacteria and Viruses. CRC Critical Reviews in Environmental Control, Vol 18, Issue 4, p. 295-314. Non-GLP, Published.	N	--
IIIA 5.4.1-03	Grier, N.	1983	Silver and its Compounds, Disinfection, Sterilisation and Preservation, S. Block, ed., Philadelphia: Lea & Febiger, p 375-389. Non-GLP, Published.	N	--
IIIA 5.4.1-04	Russell, A.D. and Hugo. W.B.	1994	Antimicrobial Activity and Action of Silver. Progress in Medicinal Chemistry – Vol 31, edited by G.P Ellis and D.K. Luscombe. Elsevier Press, p 351-370. Non-GLP, Published.	N	--
IIIA 5.7.1-01	Dollenmeier, P.	2002	The Risk of Generating Ag^+ Resistant Germs, Ciba Speciality Chemicals Inc, 6 June 2002. Non-GLP, Unpublished.	Yes	EU Silver Task Force
IIIA 5.7.1-02	Morris, C. J.	2010	Overview of Silver Antimicrobial Resistance, TSGE, Unpublished report. 16 August 2010. Non-GLP, Published.	Yes	EU Silver Task Force
Section 6					
IIIA 6.1.1-01	[redacted]	2006a	Agion Antimicrobial Type AD Acute Oral Toxicity Up and Down Procedure in Rats. [redacted]. Report No. 18636. GLP, Unpublished	Y	Sciessent
IIIA 6.1.2-01	[redacted]	2006b	Agion Antimicrobial Type AD Acute Dermal Toxicity Study in Rats-Limit Test. [redacted] Study No. 18637. GLP, Unpublished	Y	Sciessent
IIIA 6.1.3-01	[redacted]	2006c	Agion Antimicrobial Type AD Acute Inhalation Toxicity in Rats-Limit Test. [redacted]. Study No. 18638. GLP, Unpublished.	Y	Sciessent
IIIA 6.1.4-01	[redacted]	2006d	Antimicrobial Type AD Primary Skin Irritation Study in Rabbits. [redacted]. Study No. 18640. GLP, Unpublished.	Y	Sciessent

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA 6.1.4-02	[redacted]	2006e	AgION Antimicrobial Type AD Primary Eye Irritation Study in Rabbits. [redacted] Study No. 18639. GLP, Unpublished.	Y	Sciessent
IIIA 6.1.5-01	[redacted]	2015	Agion Silver Antimicrobial Type LGK: Local Lymph Node Assay (LLNA) in mice. [redacted]. Report 40546. GLP, Unpublished.	Y	Sciessent
IIIA 6.2-01	Furchner, J.E., Richmond, C.R. and Drake, G.A.	1968	Comparative metabolism of radionuclides in mammals – IV. Retention of silver-110m in the mouse, rat, monkey and dog. Health Physics Pergamon Press 1968. Vol 15 pp. 505-514. Non-GLP, Published.	N	--
IIIA 6.2-02	East, B.W., Boddy, K., Williams, E.D., Macintyre, D. And Mclay, A.L.C.	1980	Silver retention, total body silver and tissue silver concentrations in argyria associated with exposure to an anti-smoking remedy containing silver acetate. Clin Exp Dermatol. 5(3):305-311. Non-GLP, Published.	N	--
IIIA 6.2-03	Newton, D. and Holmes, A	1968	A case of accidental inhalation of Zinc-65 and silver-110m. Radiation Research 29, 403-412. Non-GLP, Published.	N	--
IIIA 6.2-04	Phalen, R.F. and Morrow, P.E.	1973	Experimental inhalation of metallic silver. Health Physics Pergamon Press 1973. Vol 24 pp. 509-518. Non-GLP, Published.	N	--
IIIA 6.2-05	Faust, R.A.	1992	Toxicity Summary for Silver. US Army Toxic and Hazardous Materials Agency. Aberdeen Proving Ground, Maryland. Non-GLP, Published.	N	--
IIIA 6.2-06	Baldi, C., Minoia, C., Di Nucci, A., Capodaglio, E. ad Manzo, L.	1998	Effects of silver in isolated rat hepatocytes. Toxicology Letters, 41, 261-268 Non-GLP, Published.	N	--
IIIA 6.2-07	Scott, K.G. and Hamilton, J.G.	Not known	The metabolism of silver in the rat with radio-silver used as an indicator. University of California Publications in Pharmacology: pp 241-262. Non-GLP, Published.	N	--
IIIA 6.2-08	Olcott, C.T.	1947	Experimental argyrosis. IV. Morphologic changes in the experimental animal. Non-GLP, Published.	N	--
IIIA 6.2-09	Olcott, C.T.	1947	Experimental argyrosis. V. Hypertrophy of the left ventricle of the heart in rats ingesting silver salts. Non-GLP, Published.	N	--
IIIA 6.2-10	Rungby, J.	1990	An experimental study on silver in the nervous system and on aspects of its general cellular toxicity. Danish Medical Bulletin Vol. 37 No 5. 442-449. Non-GLP, Published.	N	--

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA 6.2-11	Anon	1990	Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for silver Non-GLP, Published.	N	--
IIIA 6.2-12	Skog, E and Wahlberg, J.E.	1963	A comparative investigation of the percutaneous absorption of metal compounds in the guinea pig by means of the radioactive isotopes: 51Cr; 58Co; 65Zn; 110mAg; 115m Cd; 203Hg. Journal of investigative dermatology. pp 187-192. Non-GLP, Published.	N	--
IIIA 6.4.1-01	[redacted]	2001	90-Day Dietary Toxicity Study of Zeomic in Rats. [redacted] Study Number 892-001. GLP, Unpublished	Y	Sciessent
IIIA 6.4.1-02	[redacted]	2003	90-Day Oral Toxicity Study with Zeomic AK10D in Male and Female Beagle Dogs. [redacted] Project No. 354015. GLP, Unpublished	Y	Sciessent
IIIA 6.5-01	[redacted]	1992a	Combined Chronic Toxicity/Carcinogenicity Study of Zeomic in Mice and Rats. [redacted] Non GLP, Unpublished.	Y	Sciessent
IIIA 6.6.1-01	Jones, E.	1995	Novaron – bacterial mutation assay. Huntingdon Research Centre, Woolley, Cambridgeshire, UK. Report number TSI 80B/941609. GLP, Unpublished.	Y	Milliken Europe B.V.B.A
IIIA 6.6.1-02	Jones, E.	1994	Novaron – bacterial mutation assay. Huntingdon Research Centre, Woolley, Cambridgeshire, UK. Report number TSI 72/941424. GLP, Unpublished.	Y	Milliken Europe B.V.B.A
IIIA 6.6.1-03	Jones, E.	1995	Novaron – Novaron – bacterial mutation assay. Huntingdon Research Centre, Woolley, Cambridgeshire, UK. Report number TSI 80A/941612 GLP, Unpublished.	Y	Milliken Europe B.V.B.A
IIIA 6.6.2-01	Kelly, M.D.	1995	JMAC powder: *In vitro* mammalian cell cytogenicity test Chinese Hamster Ovary Cells: B10, Annex V and OECD 473 Toxicol Laboratories. Study No. M/CCA/40863. GLP, Unpublished.	Y	Clariant International Ltd
IIIA 6.6.2-02	Kelly, M.D.	1994	JMAC powder: *In vitro* mammalian cell cytogenicity test Chinese Hamster Ovary Cells: B10, Annex V and OECD 473. Toxicol Laboratories. Study No. M/CCA/38823. GLP, Unpublished.	Y	Clariant International Ltd
IIIA 6.6.2-03	Loveday, K.S.	1990c	Silver copper zeolite in vitro chromosomal aberration assay. Arthur D. Little inc. ADL Reference 63613-22. GLP, Unpublished.	Y	Fuji (Ciba Inc.)

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA 6.6.2-04	Wright, N.P.	2002	Alpha San RC2000 Chromosome aberration in human lymphocyte cells, Safepharm Labs Ltd., SPL Project Number, 656/163. GLP, Unpublished	Y	Milliken Europe B.V.B.A
IIIA 6.6.2-05	Schulz, M.	2003	In vitro Chromosome aberration test in Chinese Hamster V79 Cells with TKA 40265 (IRGAGUARD B 8000). RCC- Cytotest Cell Research GmbH, In den Leppsteinswiesen 19, Rossdorf, Germany. RCC-CCR Project No.: 759300. GLP, Unpublished.	Y	Ciba Inc
IIIA 6.6.3-01	[redacted]	1995	JMAC: OECD 476. Mutation of L5178Y mouse lymphoma cells at the thymidine kinase $TK^{+/-}$ locus. Fluctuation assay. [redacted] project number 36/42. GLP, Unpublished.	Y	Clariant International Ltd
IIIA 6.6.3-02	[redacted]	2003	Zeomic Type AK Silver Zeolite A Mammalian Cell Mutation Assay. [redacted] Study No. SZN 008/033512. GLP, Unpublished	Y	Sciessent
IIIA 6.6.3-03	[redacted]	2002	Cell mutation assay at the thymidine kinase locus (TK +/-) in mouse lymphoma L5178Y cells with TKA 40265 (Irgaguard B 8000). [redacted] Study No: 844351. GLP, Unpublished.	Y	Ciba Inc
IIIA 6.6.3-04	[redacted]	2002	Unscheduled DNA synthesis (UDS) Assay Liver: in vivo. [redacted] GLP, Unpublished.	Y	Milliken Europe B.V.B.A
IIIA 6.6.3-05	[redacted]	2000	Experimental additive 9823-37, L5178Y $TK^{+/-}$ mouse lymphoma assay. [redacted] project number 656/046. GLP, Unpublsihed.	Y	Milliken Europe B.V.B.A
IIIA 6.6.4-01	[redacted]	1998	JMAC powder: Micronucleus test in the mouse. [redacted] Report No. 036/117. GLP, Unpublished.	Y	Clariant International Ltd
IIIA 6.6.4-02	[redacted]	2000	Experimental additive 9823-37: Micronucleus test in the mouse [redacted] Study Number 656/047.	Y	Milliken Europe B.V.B.A
IIIA 6.6.4-03	[redacted]	1994	Novaron. Mouse micronucleus test. Huntingdon Research Centre Ltd, [redacted] 74/941459.	Y	Milliken Europe B.V.B.A
IIIA 6.6.4-04	[redacted]	2002	Unscheduled DNA synthesis (UDS) Assay Liver: in vivo. [redacted] GLP, Unpublished.	Y	Milliken Europe B.V.B.A

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA 6.6.5-02	[redacted]	2016	Hygentic 8000: Rat Alkaline Comet Assay [redacted]	Y	Sciessent LLC and BASF SE
IIIA 6.7-01	[redacted]	1992a	Combined Chronic Toxicity/Carcinogenicity Study of Zeomic in Mice and Rats. [redacted] Non GLP, Unpublished.	Y	Sciessent
IIIA 6.8.1-01	[redacted]	1999	Experimental additive number 9823-37: Preliminary oral gavage teratology study in the rat. [redacted] Project number 656/016. GLP, Unpublished.	Y	Milliken Europe B.V.B.A
IIIA 6.8.1-02	[redacted]	1999	Experimental additive number 9823-37: Oral gavage teratology study in the rat [redacted] project number 656/017. GLP, Unpublished.	Y	Milliken Europe B.V.B.A
IIIA 6.8.1-03	[redacted]	1990	Study of Teratology in Pregnant Rats Administered Silver-Copper Zeolite Orally. [redacted]. Report Number 63613-18. GLP, Unpublished.	Y	Fuji Ciba Inc and Ishizuka Glass Co Ltd
IIIA 6.8.1-04	Price, C.J. and George, J.D.	2002	Developmental toxicity evaluation for silver acetate (CAS No. 563-63-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 19 National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA. NTP study number TER-20-001. Non GLP, Published.	N	-
IIIA 6.8.1-05	Shavlovski, M.M. et al	1995	Embryotoxicity of silver ions is diminished by ceruloplasmin--further evidence for its role in the transport of copper. Biometals. 8(2):122-128. Silver chloride. Non GLP, Published.	N	-
IIIA 6.8.2-01	[redacted]	2002	Experimental additive 9823-37: Dietary 2-generation reproduction study in the rat. [redacted] report number 656/082. GLP, Unpublished.	Y	Milliken Europe B.V.B.A
IIIA 6.8.2-02	[redacted]	2002	A Dietary Two-Generation Reproduction and Fertility Study of Zeomic in Rats. [redacted] Study Number 892-002. GLP, Unpublished.	Y	Sciessent
IIIA 6.8.2-06	Sprando RL, Black T, Keltner Z, Olejnik N & Ferguson M	2016	Silver acetate exposure: Effects on reproduction and post-natal development, Food and Chemical Toxicology.	N	-

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA 6.10-01	Thurman, R.B. and Charles, P.G.	1989	The molecular mechanisms of copper and silver ion disinfection of bacteria and viruses CRC Critical Reviews in Environmental Control 18(4): 295-315. Non GLP, Published.	N	-
IIIA 6.10-02	Baldi, C., Minoia, C., Di Nucci, A., Capodaglio, E., and Manzo, L.	1988	Effects of silver in isolated rat hepatocytes. Toxicol Lett. 41(3):261-268. Non GLP, Published.	N	-
IIIA 6.14-01	Paternaude, L.	2015a	Protocol for the determination of silver migrating from treated LDPE after exposure to simulated human sweat and human saliva solution. Sciessent LLC Report Number AA-15-156. Non-GLP, Unpublished	Y	Sciessent
IIIA 6.14-02	Paternaude, L.	2015b	Paternaude, L. (2015): BPD Supplemental Data Submission. Microbial and Analytical Evaluation for Agion® Antimicrobial Type LGK. Sciessent LLC. Report Number: Not Stated. Unpublished.	Y	Sciessent
IIIA 6.14-03	Garraud, B.M.	2014	Protocol for the determination of silver migrating from LDPE and pillow cases after exposure into simulated human sweat and saliva media. Sciessent LLC. Report Number: Not Stated. Non-GLP. Unpublished.	Y	Sciessent
IIIA 6.14-04	Kyranos, J.N.	1991	Silver zinc zeolite: Leaching of silver and zinc from impregnated polymers. Arthur D. Little, Inc, Acorn Park Cambridge, MA, USA. ADL Reference 66365-20. GLP, Unpublished.	Y	Sciessent

DOC III Addendum – additional toxicological information					
IIIA 6.10-03	Furchner, J.E, Richmond, C.R. and Drake, G.A	1968	Comparative metabolism of radionuclides in mammals – IV. Retention of silver-110m in the mouse, rat, monkey and dog. Health Physics Pergamon Press 1968. Vol 15 pp. 505-514.	N	Public domain literature.
IIIA 6.10-04	Scott, K.G. and Hamilton, J.G.		The metabolism of silver in the rat with radio-silver used as an indicator. University of California Publications in Pharmacology: pp 241-262.	N	Public domain literature.
IIIA 6.10-05	Skog, E and Wahlberg, J.E.	1963	A comparative investigation of the percutaneous absorption of metal compounds in the guinea pig by means of the radioactive isotopes: 51Cr; 58Co; 65Zn; 110mAg; 115m	N	Public domain literature.

			Cd; 203Hg. Journal of investigative dermatology. pp 187-192.		
IIIA 6.10-06	Phalen, R.F.and Morrow, P.E.	1973	Experimental inhalation of metallic silver. Health Physics Pergamon Press 1973. Vol 24 pp. 509-518.	N	Public domain literature
IIIA 6.10-07	Newton, D. and Holmes, A	1966	A case of accidental inhalation of Zinc-65 and silver-110m. Radiation Research 29, 403-412.	N	Public Domain literature
IIIA 6.10-08	Olcott, C.T.	1947	Experimental argyrosis. IV. Morpho-logic changes in the experimental animal.	N	Public domain literature
IIIA 6.10-09	Olcott, C.T.		Experimental argyrosis. V. Hyper-trophy of the left ventricle of the heart in rats ingesting silver salts.	N	Public Domain

Section 7
Note: References related to the environmental fate and effects of silver are found in the silver core CAR
Section 8
No references submitted.
Section 9
No references submitted.
Section 10
No references submitted.

Reference list of studies not submitted
All relevant non-published references owned by Sciessent LLC have been submitted.

References added by the eCA

SCENIHR Effects of the Active Substances in Biocidal Products on Antibiotic Resistance Version of 4 November 2008

FEMS Microbiology Reviews, Special Issue: Antibiotic Resistance, Volume 35, Issue 5, pages 901–911, September 2011 and references therein.

T. J. Johnson, K. E. Siek, S. J. Johnson, L. K. Nolan, Antimicrobial Agents and Chemotherapy, Vol 49, No. 11, p 4681-4688, Nov. 2005

Section 6:

Fruijtier-Pölloth, C. The safety of synthetic zeolites used in detergents. Archives of Toxicology. 2009 Jan 1; 83(1): 23-83
HERA 2004. Human & Environmental Risk Assessment on ingredients of European household cleaning products. Zeolite A, Version 3.0, January, 2004, http://www.heraproject.com/files/8-F-04-%20HERA%20Zeolite%20full%20V3%20web%20wd.pdf
IGHRC. Guidelines on route to route extrapolation of toxicity data when assessing health risks of chemicals. (April, 2006) IGHRC Guidelines | April 2006. http://ieh.cranfield.ac.uk/ighrc/cr12[1].pdf
IPCS International Programme on Chemical Safety Poisons Information Monograph (Group Monograph) G016, 1992. http://www.inchem.org/documents/pims/chemical/pimg016.htm
Johnson T, Haseman JK, Goodman JI, Ward JM, Loughran Jr TP, Spencer PJ. Review of Large Granular Lymphocytic Leukemia in Fischer 344 Rats as an Initial Step Toward Evaluating the Implication of the Endpoint to Human Cancer Risk Assessment. Toxicological Sciences 99(1), 3-19 (2007)
McCullough MJ, Tyas MJ. Local adverse effects of amalgam restorations. Int Dent J. 2008 Feb;58(1):3-9
USEPA. Ambient Water Quality Criteria for Silver, 1980

http://www.epa.gov/nscep/index.html
A.B. G Lansdown (2010). Silver in Healthcare: Its Antimicrobial Efficacy and Safety in Use Issues in toxicology No. 6, ISBM: 978-1-84973-006-8
Attieh et al (1999), The Journal of Biological Chemistry
Guidance Notes On Dermal Absorption, Series on Testing and Assessment, No. 156 NV/JM/MONO(2011)36 Organisation for Economic Co-operation and Development 18-Aug-2011 Environment Directorate, Joint meeting of the chemicals committee and The working party on chemicals, pesticides and biotechnology
Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 4.1, June 2015
Guidance on the Biocidal Products Regulation, Volume III: Human health, Part A: Information Requirements (Version 1.1, November 2014)
Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance (Version 5.0, December 2016)
D., J., Kirkland, Statistical evaluation of mutagenicity test data. UKEMS sub-committee on guidelines for mutagenicity testing. Report. Part III (1989). Page 9
Linder, M. C et al (1998) American Journal of Clinical Nutrition, vol 67, No 5 (9655-9715)
OECD (2014), Current Approaches in the Statistical Analysis of Ecotoxicity Data: A guidance to application (annexes to this publication exist as a separate document), OECD Series on Testing and Assessment, No. 54, OECD Publishing, Paris, https://doi.org/10.1787/9789264085275-en.
RAC opinion Committee for Risk Assessment RAC Opinion proposing harmonised classification and labelling at EU level of Silver zinc zeolite (Zeolite, LTA1 framework type, surface-modified with silver and zinc ions) CLH-O-0000001412-86-90/F, Adopted 4 December 2015

Section 7:

HERA 2004. Human & Environmental Risk Assessment on ingredients of European household cleaning products. Zeolite A, Version 3.0, January, 2004, http://www.heraproject.com/files/8-F-04-%20HERA%20Zeolite%20full%20V3%20web%20wd.pdf
References related to silver are found in the core CAR for silver

Section 8:

WHO 2008. Guidelines for drinking-water quality: incorporating 1st and 2nd addenda, Vol.1, Recommendations. – 3rd http://www.who.int/water_sanitation_health/dwq/fulltext.pdf

Reference list of IIIB studies submitted (by Section No.; please note: the numbers refer to the sections of the BPD, Annex II)

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
Section 1					
No references submitted.					
Section 2					
No references submitted.					
Section 3					
IIIB 3.1.1-01 3.1.2-01 3.1.3-01 3.6-02	Shepler, K.	2001	Physical/Chemical Characteristics of Zeomic AJ10D. PTRL-West Report No. 1001W-001. Submitted to US EPA, 25 pages. GLP, Unpublished.	Yes	Sciessent
IIIB 3.2-01 3.3-01 3.4-01	Anon	2006	Part 3 - Product Chemistry for an End Use Product: Agion® Silver Antimicrobial Type AJ. Submitted to Canadian PMRA, 4 pages. Non-GLP, Unpublished.	Yes	Sciessent
IIIB 3.5-01 3.6-01	Cunningham, M.L.	2001	Physical/Chemical Characteristics of Zeomic AC10D. PTRL West Inc, Hercules, CA, USA. Project No. 1088W. GLP, Unpublished.	Yes	Sciessent
IIIB 3.7-01	Uchida, M.	2001	One Year Storage Stability of Zeomic Type AC Silver Copper Zeolite AC. Sinanon Zeomic Co. Ltd, Japan. Report No. Not stated. Non GLP, Unpublished. Confidential.	Yes	Sciessent
IIIB 3.7-02	Uchida, M.	2000	One-year Storage Stability of Zeomic® Type AJ10D, AJ10N and AJ10H. Submitted to US EPA, 61 pages. Non-GLP, Unpublished. Confidential	Yes	Sciessent
Section 4					
IIIB 4.1	See the Confidential Annex				
Section 5					
IIIB 5.10.2-01	Paternaude, L.	2015	BPD Supplemental Data Submission. Microbial and Analytical Evaluation for Agion® Antimicrobial Type LGK. Sciessent LLC. Report Number: Not Stated. Non-GLP, Unpublished.	Yes	Sciessent
IIIB 5.10.2-02	Foster, L.	2011	BPD Supplemental Data Submission. Microbial and Analytical Evaluation for Agion® Antimicrobial Type(s) AC, AJ and AK. Sciessent LLC. Report Number: Not Stated. Non-GLP, Unpublished.	Yes	Sciessent

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIB 5.10.2-03	Duan, T.	2017	Antimicrobial Efficacy Study: ISO 22196:2011(E), Measurements of antibacterial activity on plastics and other non-porous surfaces. Test Article: LDPE. Sciessent Assay Number: NBT-17-027 thru NBT-17-030. 27/01/2017. Unpublished	Yes	Sciessent
IIIB 5.10.2-04	Duan. T.	2017	Antimicrobial Efficacy Study: Simulation of Use condition with Incubation Process. Test Article: LDPE. Sciessent Assay Number: NBT-17-123 thru NBT-17-126; NBT-17-123A thru NBT-17-126A. 20/02/2017. Unpublished	Yes	Sciessent
IIIB 5.10.2-05	Duan, T.	2017	Antimicrobial Efficacy Study: Simulation of Use condition with Incubation Process. Test Article: LDPE. Sciessent Assay Number: NBT-17-259 thru NBT-17-261; NBT-17-259A thru NBT-17-261A. 22/03/2017. Unpublished	Yes	Sciessent
IIIB 5.10.2-11	Pickering, D.	2011	Performance of silverized GAC vs. silver zeolite treated GAC. Sciessent Internal Report. July 2011. Published Online.	Yes	Sciessent
Section 6					
References provided by member companies of the European silver task force for silver zinc zeolite and silver copper zeolite were used for the purpose of the present assessment. They are found in the respective CARs as specified.					
IIIB 6.7.1.2-07 (submitted in September 2016)	Garraud, B.M.	2016	Silver migration from textile fabrics, polycarbonate (PC) and acrylonitrile butadiene styrene (ABS) test coupons after exposure into simulated human sweat and human saliva solution. Sciessent LLC. Report Number: AA-16-210 and AA-16-248 Migration Study. Unpublished.	Y	Sciessent LLC
IIIB 6.7.1.2-08 (submitted in September 2016)	Anon.	2013	Polymer incorporated silver - silver release test. Ishizuka Glass Co Ltd. Report Number: Not stated. Unpublished.	Y	Ishizuka Glass Co. Ltd. (Sciessent LLC has permission to use the data relating to Zeomic AJ10D – silver zinc zeolite)
IIIB 6.7.1.2-09 (submitted in September 2016)	Garraud, B.M.	2014	Protocol for the determination of silver migrating from treated LDPE and pillow cases after exposure into simulated human sweat and saliva media. Sciessent LLC. Report Number: AA-13-334C thru 339C Migration Study. Unpublished.	Y	Sciessent LLC
No references submitted.					
Section 7					
No references submitted.					
Section 8					

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
No references submitted.					
Section 9					
No references submitted.					
Section 10					
No references submitted.					

Reference list of studies not submitted

All relevant non-published references owned by Sciessent LLC have been submitted.

Appendix VI: Confidential information

Please see separate files.