Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Silver zinc zeolite (Zeolite, LTA1 framework type, surface-modified with silver and zinc ions)

EC Number: -

CAS Number: 130328-20-0

CLH-O-0000001412-86-90/F

Adopted

4 December 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILVER ZINC ZEOLITE (ZEOLITE, LTA FRAMEWORK TYPE, SURFACE MODIFIED WITH SILVER AND ZINC IONS)

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name:	**Silver zinc zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions)**
EC number:	**-**
CAS number:	**130328-20-0**
Dossier Submitter:	**Sweden**

General response to comments on carcinogenicity and reproductive toxicity received during the public consultation on silver zinc zeolite

Since many of the comments are similar in nature, the dossier submitter has compiled a response addressing issues raised with respect to the proposals made for carcinogenicity and reproductive toxicity. Please note that most of these issues are actually addressed in the CLH report and in the confidential attachment "Doc II Appendix 4 Position Paper Canc, Repro, AEL.pdf"

Carcinogenicity:

The DS has proposed classification in category 2 based on positive trends for leukaemia in male and female rats and pituitary adenomas in female rats that are statistically significant. Objections made are primarily based on the arguments listed and addressed below.

1. The differences in tumour incidence between controls and different dose levels are not statistically significant in pairwise comparisons.
2. The tumour types observed have a high background incidence in the type of rat strain used and the incidences observed are within the range reported in historical control data.
3. The type of leukemia observed is not relevant for humans.
4. The conclusion made by the DS is influenced by results obtained in genotoxicity studies.

Response by the Dossier Submitter:

1. 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."
In this case, trend analysis is considered appropriate since the study includes several doses and, as stated in (paragraph 122), "the effect of increasing exposure may show up as an increase or as a decrease in the measured response, but not both."

2. Undisputedly, the general view is that the rat strain used (F344) is prone to develop mononuclear cell leukaemia and pituitary adenomas. In our view, this does not mean that increased incidences of these tumour types can bautomatically disregarded. The incidences is yet higher than in the concurrent controls and if the substance would act as a promoter it would be logical to observe an increase of tumours originating from cells that easily become initiated in the test strain used. Historical control data may be useful in borderline situations for instance if there is a statistical significant difference in tumour incidence at a single dose level or when there is reason to doubt the results obtained in the concurrent control group. In this case, there is not considered to be a borderline situation since a statistically significant dose-response was observed. It seems highly unlikely that the tumour incidences are higher than controls in both sexes of all dose groups (8 observations) by pure chance. The concurrent controls are sufficient in number and they do not differ significantly from the low-dose group. It is thus not considered accurate to let historical control data take precedence over the concurrent control data especially taking into account that there is no or only limited information on test conditions (e.g. strain, supplier, test facility, housing conditions, diet, group size, administration route, survival rates, assessment criteria etc).
   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.
3. The type of leukaemia is not characterised but even if the tumour type would not be relevant for humans, a substance promoting cells into tumours could have the same effect and promote human cells into the tumour types that humans are prone to develop.
4. Since there is no indication that SZZ reaches the target tissue in the in vivo genotoxicity study, the negative result is not considered reliable. Based on the low oral absorption of silver, bone marrow exposure can be expected to be minimal and the test system is thus considered inappropriate to use for the substance. Therefore, the DS concludes that data is insufficient for classification with respect to genotoxicity.
   Nevertheless, mutagenicity is a different endpoint and a separate classification category and carcinogenicity is not necessarily linked to this endpoint. Therefore, the classification proposal is only based on the results observed in the carcinogenicity

study and, as discussed above, there is rather a fear that SZZ acts as a tumour promoter.

Reproductive toxicity:

The DS has proposed classification in category 1b based on foetal/pup mortality, reduced pup weights and reduced thymus weight that are not considered secondary non-specific consequences of marked toxicity in the mother. Effects were primarily noted in F1 high dose pups (12500ppm) and F2 mid dose pups (6250 ppm). Due to the high mortality in F1 high dose animals, the group was terminated before mating. Objections made are primarily based on the arguments listed and addressed below.

1. Classification of SZZ is based on read across from a study performed with silver chloride.
2. Effects observed are being secondary to maternal toxicity manifested as mortality, reduced bodyweight gain in P0 females during gestation and lactation, maternal neglect, changes in hematological parameters or nephrotoxicity.
3. Effects are due to silver displacing copper in ceruloplasmin leading to copper depletion in mothers and fetuses.
4. Developmental toxicity is not observed in studies performed with other silver substances.

Response by the Dossier Submitter:

1. Classification is not based on the effects noted in the published study by Shavlovski. As clearly stated in the CLH report (section 4.10.6) the results of the two-generation study with SZZ is considered sufficient stand-alone data for the classification proposed. Results from studies performed with other silver containing substances (positive as well as negative) are included and discussed for transparency. The study by Shavlovski is more thoroughly discussed since the effects observed resemble those in the SZZ study and since the study proposes a plausible mechanism for the developmental toxicity observed.
2. The possible influence of maternal toxicity is extensively discussed in the CLH report in section 4.10.5.

   Mortality: There was no mortality at all in the P high dose females. Mortality was restricted to males. The mortality was indeed high in those F1 high dose females and males that survived delivery but these animals were in a poor condition from birth that deteriorated over time and the group had to be terminated before mating. Therefore, the mortality pattern of dams does not indicate a severe maternal toxicity that would explain effects observed in pups of high dose P dams and pups of mid-dose F1 females.

   Bodyweights: Bodyweight gain was reduced in high dose P females (but not in F1 mid dose females showing similar effects) during gestation. However, as discussed on page 89, if the actual body weight gain in dams is estimated by excluding the foetal weights, the bodyweight gain in dams was in fact higher than in controls. This indicate that the reduced bodyweight gain was due to reduced foetal weights rather than an effect in the dam.

Industry has included individual data on F1 mid dose dams in the confidential attachment 7 to demonstrate that effects in F2 pups were due to reduced body weight gains (week 1 and/or bodyweight gain during gestation) in dams. The DS finds no such correlation between bodyweight at week 1 and/or bodyweight gain during gestation and the presence of stillborn pups[1]. Neither were there any correlation between the number of stillborn in individual 12500 ppm P dams and the extent of bodyweight gain. Moreover, according to the OECD guidance document on mammalian reproductive toxicity testing and assessment, a feed restriction study clearly showed that severe weight loss or decrease in body weight gain per see induced minor changes in skeleton development but no effects on viability or malformations in the rat (Fleeman, 2005).

Maternal neglect: According to the study report, dams and litters were observed twice daily for behavioral alterations such as nursing. No deviations were noted except that food intake was reduced in high dose females during lactation. Considering that many of the dams lost some of their pups during the first days, the reduced food intake could solely illustrate the food demand being lower due to less lactating pups. Therefore, effects seen in pups are not considered to be due to maternal neglect but rather to result from effects occurring already during the gestation period.

Changes in hematological parameters: As discussed in section 4.7, reduced hemoglobin levels were observed in repeated dose toxicity studies but effects did not meet criteria for classification. Effects on hematological parameters were noted also in high and mid dose P animals. Since no analyses of haematological parameters were made for the other generations, the sensitivity of pups is not known.

Nephrotoxicity: As discussed on page 90, histopathological effects in kidneys were observed in treated animals with a higher incidence and severity in males. However, since there were no treatment related clinical signs in high dose females these effects are not considered to demonstrate a marked unspecific toxicity that would explain the effects observed in pups.

3. As stated in the CLH report, the DS finds the mechanism proposed by Shavlovski, i.e. silver and perhaps zinc displacing copper in ceruloplasmin and thus causing a copper deficiency in pups, plausible. However, it is not known whether this is the only mechanism for the developmental toxicity of SZZ. Besides fairly crude measurements of F2 pup homogenates, there is no data on the levels of copper, silver, zinc or iron in parental animals or pups. Therefore, it is not possible to assess if there is a copper deficiency also in the parents and/or if the copper deficiency is more pronounced in the pups. Nevertheless, since dams show no treatment-related clinical signs whereas

[1] From the table on page 4 of the attachment, it can be seen that dams 782 and 791 had no stillborn pups although the bodyweight gain was similar to dams 808, 781 and 786 who had stillborn pups. This was claimed to be due to these dams having a higher bodyweight at week 1. However, dams 788, 789, 800 and 807 had similar starting weights and similar or higher weight gain but yet stillborn pups. Dam 809 had next to lowest starting weight and intermediate bodyweight gain but did not have any stillborn pups. The applicant argues that the bodyweight data on dam 789 indicate a higher susceptibility to toxicity in this animal but this is contradicted by data on dam 803 who had comparable bodyweight data (week 1, w1-12 gain, end, day 0 and day 0-20) but no stillborn pups.

pups clearly fail to survive, the sensitivity of pups seems indeed much higher. Likewise, if effects in the pups are due to silver and/or zinc causing an iron deficiency also in the dams, pups obviously cope less well with this deficiency.

For many substances classified for developmental toxicity, the exact mechanism is not known. However, in this case, there is a very plausible specific mechanism explaining the developmental toxicity observed. Irrespective of effects are caused by silver, by zinc or by both elements and irrespective of whether or not silver and/or zinc have an direct effect or exert the toxicity by preventing copper from binding to ceruloplasmin, the consequences of exposure to SZZ is the same. Therefore, the DS proposes that this intrinsic property of the substance should be communicated to the user by classification and labelling.

4. As discussed in the CLH report, the reason why no effects were observed in the other developmental studies performed with different silver containing substances may be:
    a. effects of silver manifest above a critical silver exposure level and the exposure to silver in other developmental toxicity studies (based on silver content and release) is lower than in the study with SZZ and/or
    b. silver and zinc share the same mechanism for developmental toxicity. Therefore, due to the presence of zinc in SZZ, the critical level where effects manifest is exceeded even though the silver exposure seems to be similar in the fertility studies with SZZ and a different silver containing substance,
    c. the exposure duration is too short to completely inactivate ceruloplasmin in the blood. Shavlovski and co-workers demonstrated that effects were only observed if exposure was continuous during the entire gestation period (days 1-20). When restricted to days 7-15, effects were not observed. The exposure period in the developmental studies performed with other silver containing substances was between days 6 and day 15 (or 19 in one study)
    d. copper is present in at least one of the other silver containing substances. This may be sufficient to counteract effects of silver (and perhaps zinc) by keeping the copper level in excess of silver (and perhaps zinc) and thus preventing other metals from binding to ceruloplasmin.

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Netherlands	TNO	National NGO	1
Comment received				
Based on available data, we do not agree with the proposed classification on reprotox and carcinogenicity. Please see Specific comments for further details. *[ECHA note: The following confidential attachments were provided with the comment above:]* TNO Comment on carcinogenicity of Silver Zinc Zeolite and TNO Comment on reproductive toxicology of silver zinc zeolite.				

Dossier Submitter's Response
Please note that TNO is acting as consultant company for one of the companies participating in the silver task force. Objections to the classification proposal made in the attached documents are principally based on arguments that tumour types observed in the carcinogenicity study are within ranges observed in historical control data (carcinogenicity) and developmental effects in the fertility study are toxic effects and/or consequences of maternal toxicity. Since these arguments have been put forward by other parties as well, we have made a general response in which these are discussed. This response is presented as an introduction to this RCOM table.
RAC's response
RAC considers that the weight of the evidence provided is not sufficient to support classification as carcinogenicity category 2, mainly due to the weak statistical significance of the reported incidences of leukaemia and pituitary adenomas without carcinomas, as well as the doubts about human relevance of the leukaemia reported in rats, the low number of tumours/animal in exposed group, the similar survival between exposed and non-exposed animals and the apparent sex-dependence of the reported tumours. RAC has concluded that classification as Repr. 2 (H361d) is warranted because the criteria for this category are fulfilled. RAC further notes that the reported mechanisms of developmental toxicity based on the depletion of copper bioavailability due to its displacement from ceruloplasmin seem to be plausible and relevant for humans.

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2015	United Kingdom	European BPR Silver Task Force	Industry or trade association	2
Comment received				
The European BPR Silver Task Force does not agree with the decision of the Swedish Chemical Agency (KemI) to propose silver zinc zeolite as a Category 2 Carcinogen and Category 1B for reproductive toxicity. The available data do not support classification for these hazardous effects. The scientific arguments justifying non-classification are provided in the attached detailed expert opinions. The key arguments are summarised below as specific comments. *[ECHA note: The following confidential attachments were provided with the comment above:]* • EU Silver Task Force expert opinion on the carcinocenicity and reproductive toxicity potential of silver and AEL derivation • Carcinogenicity of Silver Zinc Zeolite • Reproductive Toxicology of Silver Zinc Zeolite • Carcinogenic and Teratogenic Potential of Silver Zinc Zeolite • Evaluation of a two-generation study with silver zinc zeolite • Reproductive and developmental toxicity of siver zinc zeolite				
Dossier Submitter's Response				
Objections to the classification proposal made in the attached documents are principally based on arguments that tumour types observed in the carcinogenicity study are within ranges observed in historical control data (carcinogenicity) and developmental effects in the fertility study are toxic effects and/or secondary to maternal toxicity. Please note our general response to these comments on the first page of this RCOM table.				

RAC's response
Please, see RAC response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2015	United States	Silver Task Force North America	Industry or trade association	3

Comment received

The following are comments on classification recommendations, based upon the evaluation by the Swedish Chemicals Agency (KemI) as the Competent Authority of the rapporteur state, that the STF North America considers to be of concern and not supported by the available scientific evidence.

[ECHA note: The following attachment was provided by Silver Task Force North America: Evaluation of Silver Substances under Regulation 528/2012]

Dossier Submitter's Response

According to information on page 45, this attachment is not claimed to be confidential. Please find the DS response below structured according to the sub-headings used in the attachment:

Argyria: STF claims that argyria is not generally considered an adverse effect. It should be noted that argyria is the effect driving reference values set by US EPA and for sodium thiosulfate under 1107/2009. In response to the comment on reference values used for the silver ion equivalents under the BPR, although not relevant for classification, it should also be noted that the external oral reference value (the BPR value is a systemic value) is similar to the value set by US EPA.

Dermal absorption: This parameter is important for risk assessment and when comparing effect levels via different exposure routes but it is, in our view, less important in the context of classification. However, the DS would like to inform that the value concluded in the BPR is based on the data considered to be of highest reliability and relevance. The information on dermal absorption in the review by Hostynek (2003) is restricted to the sentence "experiments to determine the penetration of human skin by water-soluble silver salts have not given measurable results". It is unclear to the DS from which references the author has based his conclusion upon and it is thus also unclear if the silver compound, dose levels or test conditions used are relevant for the risk assessment of SZZ.

Carcinogenicity: Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.

In addition, the DS would like to add the following information to some specific statements made above:

The US EPA has evaluated the carcinogenicity study and the assessor concludes (on p 40): "our reviewer believes that these dose-response trends may be linked to treatment and the use of a higher dose may have better linked the treatment to tumour incidence."(http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-072503_28-Aug-02_006.pdf).

The reason for proposing classification Carc. 2 is because the DS did not consider it safe to disregard the results showing statistically significant positive trends for leukaemia and pituitary adenomas. A trend is a stronger indication of the relevance of an effect and it seems unlikely that this would appear by chance in both sexes (leukaemia).

The absorption of orally administered silver is low (below 5%) thus bone marrow exposure can be expected to be minimal (supported by results from the in vivo genotoxicity study with SZZ). However, the bone marrow is a test system and the absence of mutagenicity due to lack of exposure only means that the test system is inappropriate to use for the

substance. It does not prove that SZZ lacks mutagenic potential in tissues exposed to a higher degree (e.g. GI tract, liver). Nevertheless, mutagenicity is a different endpoint and classification category and carcinogenicity is not necessarily linked to this endpoint. There is rather a fear that SZZ acts as a tumour promoter that turns initiated cells into those tumour types the species exposed is prone to develop. In Fischer rats, these include leukaemia and pituitary adenomas whereas humans are more prone to develop other types of tumours.
Reproductive toxicity: Please note our general response to comments received on reproductive toxicity on the first page of this RCOM table. The DS reiterates that the classification proposal for reproductive toxicity is based on data on silver zinc zeolite. The published study with silver chloride is considered as supporting information providing further information on a plausible mechanism.

RAC's response

RAC does not consider argyria an adeverse effect sufficiently severe that it would trigger classification and therefore RAC does not propose classification for STOT RE.
Dermal absorption is relevant for risk assessment but is not critical for hazard identification or repeated dose toxicity when all categories have been assessed on the basis of oral studies.
Regarding carcinogenicity and developmental toxicity, please see RAC response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	Germany		MemberState	4

Comment received

The assessment of the RMS Sweden of Silver Zinc Zeolite (CAS 130328-20-0) has been previously evaluated and commented on during the peer-review procedure for approval of the biocidal active substance. This includes an e-consultation specifically on the issue of mutagenicity and carcinogenicity.

However, silver zinc zeolithe is one of many SCAS (silver containing active substances) and there may be differences in silver content between silver zinc zeolithes. In order to account for resulting differences in potency and additivity when combined with other SCAS, specific concentration limits (SCL) should be proposed for all classifications. These SCLs should relate to silver content / release.

Dossier Submitter's Response

It is correct that the hazard assessment has been peer reviewed (including an electronic consultation on carcinogenicity, mutagenicity was discussed at a Technical Meeting) under 98/8. This is described in section 2.1 of the CLH report.
There are certainly more silver zinc zeolites than the three types included in this classification entry commercially available, by that the elaborated chemical name in section 1.1. The silver exposure from SZZ depend on silver content and release which in turn depends on several factors including the zeolite structure; the type of ions present, the pore size, chemical modifications etc. Therefore, if a SCL should be set relating to silver, it should be based on the silver exposure factor, i.e the product of silver content and release, of the SZZ used in the particular study.
However, we hesitate to set SCL for the purpose of equivalence and additivity since, with the possible exception of pigmentation, it is not possible to conclude from existing data if the effects considered to meet criteria for classification can be ascribed to silver only.
In addition, according to CLP guidance, additivity is not applicable to most of the hazard classes that SZZ is proposed to be classified in:
"Non-additivity is applied for the following hazard classes:

a. skin and respiratory sensitisers;
b. germ cell mutagenicity;
c. carcinogenicity;
d. reproductive toxicity;
e. specific target organ toxicity, single and repeated exposure, categories 1 and 2;
f. aspiration hazard (plus consideration of viscosity of the final mixture);
g. skin corrosion/irritation in some special cases (see CLP Annex I, 3.2.3.3.4); and
h. serious eye damage/eye irritation in some special cases (see CLP Annex I, 3.3.3.3.4).”
Although setting of SCL above the GCL could be considered for potency, we doubt that this is possible from the data available. According to the CLP guidance this is possible in exceptional cases if there is robust data supporting identification of SCL. However, as an example, the reproductive toxicity data available is a two-generation study with type AK. The effects noted in this study is considered sufficient stand-alone data to propose classification for developmental toxicity in category 1B but in the absence of any developmental toxicity studies in rat or rabbits it is not considered safe to exclude that effects would occur at doses below those tested in the two-generation study with type AK. Moreover, we wonder whether this is correct from a procedural point of view considering that the public consultation is closed.

RAC’s response

RAC agrees with the position of the DS (as stated above) that setting an SCL is not appropriate in this case. RAC has concluded that classification as Repr. 2 (H361d) is warranted for reproductive toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	United Kingdom		MemberState	5

Comment received

Could it please be clarified whether this CLH Report is really on a single substance (i.e. elemental or ionic silver) or on a mixture? The Dossier Submitter has used the maximum content of silver in silver zinc zeolite of 6% to re-calculate ecotoxicity results, however the data on zinc (which comprises up to 16%) and other components have not been included in any mixture calculations and data on the actual mixed product have been discounted. It may well be that the zinc, zeolite and other components are of such relatively low ecotoxicity that they won’t affect the conclusion - but, in effect, this CLH Report is then solely a review of the classification of silver. We are unclear whether separate CLH reports should be required on various mixtures of silver with other substances and feel that the classification of silver should probably be considered separately - taking into account all lines of evidence coming from various forms of the metal (inc. potentially nano-forms). We are also concerned that this first CLH review just of silver in silver zinc zeolite could set inappropriate precedents which could cause later problems and have wide-ranging ramifications for other forms of the substance and in other regulatory areas. Ideally all forms of silver and all up-to-date sources of reliable information on it should be considered together. There should also be closer coordination with any reviews under other chemicals legislation (e.g. biocides, WFD, REACH) so that all relevant data can be considered and harmonised regulatory endpoints for silver can be universally agreed. The same could be said of the zinc and other components.

Dossier Submitter’s Response

In our view, the need for classification of different silver containing substances must be assessed for each substance in separate CLH dossiers. From a toxicological point of view, it is quite clear that the intrinsic hazards of silver zinc zeolite are likely to differ from those of

a substance such as silver nitrate, the reaction mass of titanium dioxide and silver chloride or elemental silver in bulk or nanoform. Therefore, this classification entry considers silver zinc zeolite, not silver. Data available on other silver containing substances has been included only if considered relevant for the assessment of SZZ.
Our understanding of the process is that if additional data that is robust and relevant for silver zinc zeolite is identified (e.g under WFD ,REACH) and the DS is unaware of this information, it should be submitted during the public consultation.
The environmental hazard classification is made for silver zinc zeolite, in line with the CLP guidance chapter IV.5 for metal compounds. The classification is based on the ecotoxicity of the dissolved metal ion, which then is recalculated to the content of the metal ion in the compound. Silver zinc zeolite could also be seen as a zinc compound. However, we cannot see how this would change the proposed classification. Zinc ions are much less toxic than silver ions, so zinc does not contribute substantially to the toxicity of the compound, even if considering the higher zinc content in the zeolite. Table 32 contains a comparison of ecotoxicity between silver and zinc.
Please note, this classification is made as a requirement for the approval of the biocidal active substance silver zinc zeolite. This report does not attempt to classify silver.

RAC's response

RAC agrees with the dossier submitters response.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	France		MemberState	6

Comment received

p7, Part A – impurities and p16 Table 7
Heavy metals which are impurities that can be present in the substance have not yet been quantified. Further data are required in the biocidal dossier for the end of the year 2015. This should impact the classification of the substance.

Dossier Submitter's Response

In our opinion, this cannot be considered at present. In case this data unexpectedly shows that contaminating heavy metals do have an impact on the classification proposal in this dossier then a new CLH dossier must be prepared.

RAC's response

RAC agrees with the dossier submitters response.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United States	Fuji Chemical Industries, Ltd.	Company-Manufacturer	7

Comment received

The attached document sets forth (with references) more complete comments on the subject report.
SZZ is an ion-exchange carrier, invented nearly 40 years ago, that enables incorporation of slowly-eluted silver cation Ag+ into otherwise unaccepting organic matrices. Uses (pp 20-21) are primarily for protection of organic polymer materials, including food-contact materials. Direct application to or ingestion into the human body are not anticipated.
The Report's more stringent recommendations are based on data, often inconclusive, from studies in different (non-human) species (rat, mouse) of effects from very high doses of a different species of silver (dichloroargentate, ClAgCl-, not Ag+), resulting from dissolution of normally insoluble forms of silver (SZZ, AgCl) delivered over extended periods, in large

quantities, directly into the highly acidic, high-chlorine environment of the murine stomach. Dosage relationships are often absent or ambiguous, so mechanism and causation are unclear. Consideration of exposure and actual risk are insufficiently addressed. Extrapolation to effects of Ag+ in the uses listed (pp 20-21) is thus inappropriate, and insufficiently supported, particularly as regards carcinogenicity and reproductive toxicity. It should be noted that formation of dichloroargentate (rather than silver cation) in gastric acid has been overlooked by most of the industry, and probably consequently, by Kemi.

[ECHA note: The following attachment was provided with the comment above: Comments on CLH Report: Proposal for Harmonised Classification and Labelling (Swedish Chemicals Agency regarding Silver Zinc Zeolite, April 13, 2015)]

Dossier Submitter's Response

Please find the DS response below structured according to the subheadings used in the attachment:

Silver zinc zeolite:

We appreciate the clarification made with respect to the properties and mechanisms of ion exchange materials. However, while it certainly is beneficial to have as much detailed information on these zeolites as possible, we do not see that the information in the attachment would significantly affect the assessment made based on existing information.

Dose effects and risk: The hazard assessment is made based on the intrinsic properties of the substance and does not take exposure or actual risk into account (these factors are considered in the risk assessment).

The hazard assessment is based on the data on silver zinc zeolite that were submitted to meet the data requirements for biocides. As stated in the CLH report, there is no detailed data available with respect to the fate in the gastrointestinal tract of the particular types of silver zinc zeolites considered here. Therefore, the specific forms of silver absorbed and the exact extent of oral absorption is not known. It is assumed that silver ions released will form the same ionic forms in the GI tract regardless of the parent silver substance. For transparency, the CLH report informs about absorption data from an industry-sponsored review on zeolites. However, in the absence of detailed information this secondary information, which considers zeolites in general and not silver zinc zeolite, is not considered sufficiently robust to determine oral absorption. Nevertheless, it is used in a weight of evidence approach to support the assumption that oral absorption of the zeolite part is lower than that of silver (i.e. 5%).

There is no suspicion of industry motivation, emphasis is put on robustness and reliability of data and the majority of studies in the hazard assessment are in fact industry-sponsored GLP/guideline studies.

Carcinogenicity: In the absence of robust data on the fate in the gastrointestinal tract of those particular types of silver zinc zeolites considered here the primary ionic forms of silver is not known. Nevertheless, to assess the intrinsic properties of silver zinc zeolite, it is not crucial to know what ionic form of silver (or even Zn) is responsible for the effects observed. This may be important for read across but in the absence of other information, it is assumed, as is also made in this attachment, that silver released will form the same ionic forms in the GI tract regardless of the parent silver substance.

Reproductive toxicity: With respect to the EPA reviews referred to in the attachment, it should be noted that the US EPA assessors acknowledges the same effects as the DS in both the carcinogenicity study and in the reproductive toxicity study although the carcinogenicity study was considered unacceptable due to methodological deficiencies in the study including the lack of a MTD*. Classification is not considered in these reports.

Carcinogenicity, on p 40: *"our reviewer believes that these dose-response trends may be linked to treatment and the use of a higher dose may have better linked the treatment to tumor incidence."*

Reproductive toxicity, p 3: *"The LOAEL of 6250 ppm [..] is based on a decrease in the Live Born Index and an increase in the Stillborn Index in both the P and F1 dams. Individual pup weights were decreased at 6250 ppm on days 14 to 26 and at 12, 500 ppm on days o to 26. [..]" The LOAEL for pup toxicity was 6250 pp, [..] based on decreases in thymus weight (absolute and relative to body and brain weight).*
*http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-072503_28-Aug-02_006.pdf.
http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/cleared-reviews/reviews/072503/072503-007.pdf

RAC's response

Thank you very much for the clarification of the nature of silver zinc zeolite.
RAC highlights that in the CLH regulation an assessment of risk is not conducted for hazard identification and therefore considerations regarding exposure are not relevant.
Regarding carcinogenicity and developmental toxicity, please see RAC response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Sinanen Zeomic co. Ltd.	Company-Manufacturer	8

Comment received

Since its foundation in February 1984, Sinanen has been manufacturing and selling silver zinc zeolite as an antimicrobial for about 30 years. Sinanen ship not only within Japan, but also to a number of overseas companies in Asian countries and the United States, where products of various kinds of fields are sold. No health hazard has been reported so far by our staff in manufacturing department, product processers or users of our products.

Among the products treated with SZZ as an antimicrobial are medical appliance, cosmetics and quasi-medicines. These products include those on which the competent authorities in Japan carried out rigorous tests based on various safety-related data before commercialization. No health hazard has been reported on any of these products.

Based on the carcinogenic and reproductive test reports and a detailed analysis data, SZZ can be scientifically determined to be a substance "unable to classify" according to CLP standard.

Detailed comments are included in the attached position document.

[ECHA note: The following confidential attachment was provided with the comment above:]
Comments on the proposal for Harmonized Classification and Labelling of Silver Zinc Zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions) according to Regulation (EC) No 1272/2008 (CLP Regulation)

Dossier Submitter's Response

Response to the comment above, the attachment above and the three additional confidential attachments referred to therein(4, 5, 9):
The hazard assessment and classification proposals made are based on the intrinsic properties of the substance and does not take exposure or actual risk into account. Therefore, the migration limits considered safe by EFSA for food contact materials are not relevant for classification. In the absence of detailed information on factors such as the type of exposure, test substance, exposure levels, number and medical history of exposed population in manufacturers, the statement that no health hazard has been reported cannot be scientifically evaluated and considered in the hazard assessment.

The DS would like to stress, in response to the expert statements referred to in the attachment, the following considerations:
•As stated in the CLH report, the fertility study on szz is considered to be sufficient as stand-alone data for the classification proposal Repr. 1B. The study by Shavlovski is considered supportive information providing a plausible mechanistic explanation for the developmental toxicity observed, i.e. a copper deficiency.
•Based on the results in the latter study, the dosing period seem to be important. If the dosing period is restricted to the period of organogenesis only, as in the developmental studies performed with other SCAS, the developmental effects observed when exposure is continuous during the entire gestation period do not manifest.
•The systemic exposure to ionic forms of silver do not only depend on silver content and oral absorption. It likely depends also on the rate of silver release and the presence of additional elements such as other metals.
•We note that the experts agree with the DS in that the foetal effects observed are likely due to copper deficiency. Moreover, the expert states in confidential attachment 5 "It is thus demonstrated that developmental toxicity of SZZ is a secondary consequence of lower serum copper levels. Therefore there is only a developmental hazard when a silver containing compound such as SZZ lowers serum copper". The DS reiterates the position that classification is based on intrinsic hazard and does not take exposure and risk into consideration. Moreover, it is the DS opinion that classification is intended to inform users on potential hazards of a substance. For the pregnant user it is less important to know if developmental effects are caused by the silver ion directly or if they are due to interference with copper. The mother and the foetus should be considered a unit and in our view the copper deficiency is not a "secondary non-specific consequence of other toxic effects" but a rather specific consequence of SZZ exposure.
•The mortality and severe kidney effects observed in high dose F0 animals were restricted to males. The bodyweight gain during pregnancy was indeed reduced in high dose dams but as discussed in the CLH report, data indicate that this was due to lower foetal weights. Gravid uterus weight was not reported but when estimated from existing data, the bodyweight gain in dams was in fact higher than in controls.
•Experts state that high dose F0 females failed to gain weight as expected. This is not understood from table 12 of the original study. While bodyweight change during lactation was lower for days 0-4 and 7-14 (stat sign), the bodyweight change was in fact higher in high dose females on days 4-7, 14-21, 21-26 (stat sign) and days 0-26 than in controls. The lower bodyweights (max 11% day 14) in high dose females could be a consequence of dams having less pups and thus producing less milk. Nevertheless, this data is not considered to indicate a severe maternal toxicity in F0 females as concluded by the experts.
•The general condition of surviving F1 pups deteriorated with time and resulted in termination of this group. The absence of a high dose group complicates the assessment of the results for the F1 parents and the F2 generation.

The significance of maternal toxicity and historical control data are further discussed in the general response to comments on reproductive toxicity and carcinogencity on the first page of this RCOM table.

RAC's response

Please see RAC response to comment number 1.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILVER ZINC ZEOLITE (ZEOLITE, LTA FRAMEWORK TYPE, SURFACE MODIFIED WITH SILVER AND ZINC IONS)

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Netherlands		MemberState	9

Comment received

General comments
In general, the document is not always clearly written. For example, it often refers to silver zinc zeolite as "compound" or "substance". In other cases compound or substance however refers for example to silver nitrate. It would have been preferable that the word compound or substance is used as little as possible and the actual name of the compound or substance is used. Another example is the use of the abbreviation ERV, it can be assumed that Ecotoxicity Reference Value is meant but an explanation of the abbreviation is not given in the report.

The proposed name of this group for Annex VI is very general and other substances may also considered to be part of this group although they may have much lower silver and/or zinc content. Therefore, it is suggested to specify the substance name further for example by providing concentration ranges for silver and zinc.

The justification for read-across should be further specified by route and exposure duration. For example, for eye and skin irritation the release rate of silver and or zinc at local pH over the required exposure duration may be the determinative factor whereas for oral uptake the release within 2 hours at pH ±1.5 may be determinative.

MSCA comments for Human Hazard only.

• NL doubts the validity of classification for carcinogenicity. More information is needed on the type of leukemia observed as well as a thorough analysis of the mechanism of action and the human relevance of the findings in this strain of rats.
• NL agrees with classification for reproductive toxicity, but requests further discussion on which classification is most appropriate.
• NL request more argumentation why the read-across between the different zeolite forms is valid, considering the differences in local effects.
• NL asks for a clearer conclusion on nephrotoxicity.
• NL disagrees that pigmentation is an adverse effect and does not consider this effect sufficient for classification.

MSCA comments for Environmental Hazard only.

• NL agrees with the proposed classification for silver zinc zeolite.
• NL cannot support the statements mentioned under Section 5.3 Aquatic bioaccumulation of the CLH report, that the compound will not pass biological membranes as the substances is also classified Repr. 1B on the basis of dietary studies.
• NL is in the opinion that more ecotoxicity data are available which should be assessed and for completeness in the response should be indicated if these data would influence the classification.
• NL agrees that the classification should be based on the toxicity data for silver. However, NL is of the opinion that it should not be argued that the zeolite part is likely to remain in the polymer matrix since it is also stated to be applied topically onto materials.

Dossier Submitter's Response

General:
Editorial: We note the amendments proposed with respect to the terminology used for the

types of silver zinc zeolites and other silver containing substances.
Name: This entry considers the three types of silver zinc zeolites described in part B, section 1 of the CLH report and the concentration ranges of silver and zinc covered is actually specified in part A, section 1.1. Our understanding of the process is that if it is being claimed that this classification should not apply to a silver zinc zeolite containing less silver and zinc then, formally, a separate CLH dossier must be submitted for this substance.

Human health hazard:
Carcinogenicity: The type of leukaemia is not specified in the original report thus to our knowledge, there is no further information to add with respect to mode of action and human relevance.
In our opinion statistically significant positive trends, which give stronger support for a significance of effect than statistical significance in pairwise comparisons, cannot be dismissed. Considering that there is an increase of tumour types that the strain is prone to develop, the substance may act as a promoter of cells that easily become initiated. While this rat strain is prone to develop leukaemia and pituitary adenomas, tumours may arise from other types of initiated cells in humans upon tumour promotion.
Reproductive toxicity: Please note our general response on the first page of this RCOM table.
Variations between results from different irritation studies are not uncommon even when performed with a single substance. Usually this does not prevent taking a decision on classification.
There is no appropriate bridging data for repeated dose toxicity endpoints (STOT, C, R) for the three silver zinc zeolites. Carcinogenicity rat data is available for type AJ but the highest dose used in this study is approximately the level used as the low dose in the 90 day rat study with type AK and results are thus difficult to compare. Nevertheless, effects noted in these studies are similar (i.e. pigmentation and effects on blood parameters). Therefore, it is considered realistic to assume, as a worst-case, that effects noted with one of these SZZ will be observed if tests are conducted with the other two SZZ considered in this entry.
Nephrotoxicity: Nephrotoxicity is discussed on page 59 in the CLH report and the conclusion made is stated in section 4.7.2 (i.e. a proposal for classification STOT-RE 2). The proposal is based on nephrotoxicity (and pigmentation) observed in several species that occurred in the rat at doses close to the guidance value range. Consequently it is concluded that although the LOAEL for nephrotoxicity cannot be set (effects were seen at the lowest dose level) and it is thus not known if effects occur within the guidance value range, criteria are considered fulfilled since values are intended for guidance, not as demarcation values.
Pigmentation: The DS considers accumulation of a heavy metal in organs and tissues to be an undesired effect that should be communicated to the user through classification and labelling. Pigmentation was considered the critical effect for the LOAEL/NOAEL set for sodium silver thiosulfate under 1107/200 (for which the NL was the rapporteur) and the basis for the classification proposed in the DAR (R33 which translates into STOT-RE). See EFSA Journal 2013;11(10):3136.

The environmental hazard classification is made for silver zinc zeolite, in line with the CLP guidance chapter IV.5 for metal compounds. The classification is based on the ecotoxicity of the dissolved metal ion, which then is recalculated to the content of the metal ion in the compound. Silver zinc zeolite could also be seen as a zinc compound. However, we cannot see how this would change the proposed classification. Zinc ions are much less toxic than silver ions, so zinc does not contribute substantially to the toxicity of the compound, even if considering the higher zinc content in the zeolite. Table 32 contains a comparison of ecotoxicity between silver and zinc.
Please note, this classification is made as a requirement for the approval of the biocidal active substance silver zinc zeolite. This report does not attempt to classify silver.

RAC's response
RAC does not consider argyria an adverse effect sufficiently severe that it would trigger classification and therefore RAC does not propose classification for STOT RE. Regarding carcinogenicity and developmental toxicity please see RAC response to comment number 1. The read-across was previously considered valid under the biocide regulation. The read-across justification is provided under the section "General comments" in the opinion. Confidential documents submitted by the Industry reported severe differences in the silver release depending on the conditions of the media (pH, salinity, time and surface of exposure, etc.). Therefore, RAC considers that the differences in the vehicle (water versus saline) among the different studies for dermal acute toxicity might explain the reported differences. Environment: Noted.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Japanese Society of Industrial Technology for Antimicrobial Articles	Industry or trade association	10
Comment received				
A statement from the Japanese Society of Industrial Technology for Antimicrobial Articles is provided. *[ECHA note: The following attachment was provided with the comment above:* Public Comment Opinion on the Review of Silver Zinc Zeolite under the European Biocidal Products Regulation]				
Dossier Submitter's Response				
The hazard assessment made is based on the intrinsic properties of the substance and does not take exposure or actual risk into account. Therefore, the statement is not considered to add any new information of relevance for classification.				
RAC's response				
RAC agrees with the DS's response.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Chinese Industry Association for Antimicrobial Materials	Industry or trade association	11
Comment received				
A statement from the Chinese Industry Association for Antimicrobial Materials is provided. *[ECHA note: The following attachment was provided with the comment above:* Opinion on the Review of Silver Zinc Zeolite under the European Biocidal Products Regulation]				
Dossier Submitter's Response				
The hazard assessment made is based on the intrinsic properties of the substance and does not take exposure or actual risk into account. Therefore, the statement is not considered to				

add any new information that is of relevance for classification.
The types of silver zinc zeolites covered by this entry is described in the section on identity. Our understanding of the process is that if there is a claim that this classification should not apply to a certain silver zinc zeolite, formally, a separate CLH dossier must be submitted for this substance.

RAC's response

RAC agrees with the DS's response.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Belgium	Precious Metals & Rhenium consortium c/o European Precious Metals Federation	Industry or trade association	12

Comment received

Evidence taken into account in support of a proposed carcinogenicity classification for SZZ of Carc 2; H351 is mainly based on the finding of a positive trend for leukemia in an oral route lifetime study in one species (F344 rat). Interpretation of the occurrence of leukemia in the F344 rat is particularly problematic, such that many reviewers have questioned its relevance in this rat strain to human risk assessment. A mouse bioassay performed on SZZ did not provide any supporting evidence of carcinogenic potential. None of the individual constituents of SZZ (LTA zeolite, zinc and silver) have previously been associated with clear carcinogenic effects in either experimental animals or humans.

For further details / justification, please refer to the attached document, pages 13-14.

[ECHA note: The following attachment was provided with the comment above:
Comments on the Proposal for Harmonised Classification and Labelling for Silver zinc zeolite By the Precious Metals and Rhenium Consortium (PMC)]

Dossier Submitter's Response

Due to the extent of this attachment which comprises 57 pages, it is difficult to respond to all arguments put forward. However, the discussion mainly focus on how to interpret effects in carcinogenicity and reproductive toxicity studies and how these should be compared with classification criteria and on the following claims made:

- effects of silver arise due to a copper deficiency resulting from silver binding to copper transport proteins
- some effects observed in studies with silver zinc zeolites resemble those observed with non-substituted zeolites and are thus caused by the zeolite rather than silver or zinc
- silver impacts on the intestinal flora which results in severe gastroenteritis and thus contributes to a general disruption of homeostasis with an impairment of ETE metabolism on a broad scale in the GI tract

Please find below our response to these topics:
Objections to the interpretation of findings and the classification proposal made are principally based on arguments that tumour types observed in the carcinogenicity study are within ranges observed in historical control data (carcinogenicity) and developmental effects in the fertility study are toxic effects and/or consequences of maternal toxicity. Please refer to our general response to these comments on the first page of this RCOM table.

- We agree that there is a substantial amount of data demonstrating that silver can displace copper in enzymes resulting in a copper deficiency in foetuses. This specific mechanism of silver results in severe developmental effects regardless if silver has a direct or indirect effect. Moreover, it is not known whether or not this is the only mechanism for the foetal toxicity observed with SZZ. Please note that the classification proposal for reproductive toxicity is based on data on silver zinc zeolite. The published study with silver chloride is considered as supporting information providing further information on a plausible mechanism.
- this classification entry covers certain types of silver zinc zeolites hence the classifications proposed for the human health hazard classes are based on substance-specific information on the intrinsic hazards of this type of silver zinc zeolite. Therefore, in this respect it is less relevant if effects are due to the presence of silver, zinc, zeolite or other components of the substance. For transparency and to compare effects observed, data on other silver substances are included and discussed where relevant but read across to this data has not been applied in the CLH report.
- according to the publication referred to, silver acetate had, in gene expression studies, an effect on the representative bacterial population in ileum. However, the authors conclude *"the potential health effects of these observed changes are unknown and should be investigated further"*. Gastroenteritis was considered the cause of death of rats in this published study however this was not an effect observed among the rodent studies with silver zinc zeolite discussed in the CLH report (vomiting occurred in dogs). Therefore, we do not see how this information should be taken into consideration in this context.

RAC's response

Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Netherlands	TNO	National NGO	13

Comment received

No human data are available on the carcinogenicity of silver zinc zeolite.
Only data on two carcinogenicity studies performed with rats and mice are available.
The chronic toxicity and carcinogenicity study in B6C3F1 mice did not show any increase in incidences of tumours in treated animals as compared to untreated controls.
The chronic toxicity and carcinogenicity study in Fischer344 rats demonstrated significant positive trends for leukemia in males and females, pituitary adenomas in females and endometrial stromal polyps in the uterus. All the incidences of these malignant (leukemia) and benign (adenomas and polyps) tumours appeared to be within the ranges of historical control incidences of these tumours in untreated controls of this strain and age.
For detailed justification, please see attached confidental document.

[ECHA note: The following confidential attachments were provided with the comment above:] TNO Comment on carcinogenicity of Silver Zinc Zeolite and TNO Comment on reproductive toxicology of silver zinc zeolite.

Dossier Submitter's Response

Please note that TNO is acting as consultant company for one of the companies participating in the silver task force.
Please note our general response to comments received on carcinogenicity on the first page

of this RCOM table.
RAC's response
Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2015	United Kingdom	European BPR Silver Task Force	Industry or trade association	14

Comment received

Carcinogenicity - CLH Report Section 4.9, page 66 to 72
The eCA proposes carcinogenicity classification for silver zinc zeolite (Carc 2; H351). The eCA finds a positive statistical dose relationship for leukaemia (m/f) and pituitary adenomas (f) in an oral route lifetime study with silver zinc zeolite in one species (F344 rat).
Concluding classification solely on this statistical evidence is not sufficient evidence in the presence of other more important factors in the available data which can adequately explain the effects seen:
a) leukaemia and pituitary adenomas are only significant effects according to a dose relationship calculated by the eCA, the effects at each dose level are not significant when compared to the concurrent controls.
b) the incidence of leukaemia and pituitary adenomas seen in the treated groups is almost exclusively lower than the historical control incidence and the concurrent controls are unusually low compared to historical values. The apparent statistical significance is a product of the generally low level of effects seen in the rat study.
c) the type of mononuclear cell leukaemia seen in the F344 rat in this study is common in this rat strain and histologically comparable tumour types are not seen in humans. The incidence of leukaemia in F344 rats is increased by a number of substances that are concluded as non-carcinogenic.
d) a corresponding oral route lifetime study with silver zinc zeolite was conducted in mice and no effects were seen. Emphasis for the classification decision should be placed on the mouse data as background incidence for effects is low in this species. The mouse is better able to detect true effects as high background variability is removed.
Expert judgement should be used in the data interpretation of the available data rather than relying solely on statistical interpretation to conclude classification. Silver zinc zeolite should not be classified for carcinogenicity.

[ECHA note: The following confidential attachments were provided with the comment above:]

- EU Silver Task Force expert opinion on the carcinocenicity and reproductive toxicity potential of silver and AEL derivation
- Carcinogenicity of Silver Zinc Zeolite
- Carcinogenic and Teratogenic Potential of Silver Zinc Zeolite

Dossier Submitter's Response

Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.
For clarity, a statistically significant dose-response for leukemia and pituitary adenomas was identified also by the study author, not only by the eCA. Compared to statistically significant differences between controls and single dose levels, a trend is a stronger indication of the relevance of an effect since the entire dose-response curve is taken into consideration in such analysis.

RAC's response
Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2015	United States	Silver Task Force North America	Industry or trade association	15

Comment received

KemI propose GHS classification as Category 2 for carcinogenicity. This proposal is not supported by the available data and weight of evidence supporting the lack of carcinogenic effects of silver. The interpretation of the carcinogenicity data relies on questionable statistical interpretations without taking into account biological significance, dose-response relationship or plausibility. In this respect it is notable that neither zinc nor silver are considered to be carcinogenic and zeolite is toxicologically inert

KEMI concluded that a carcinogenicity study with silver zinc zeolite in the rat (Takizawa, 1992) showed an increase in leukemia in treated animals despite the absence of a statistically significant difference at any dose level. No increase in tumor incidence at any site was found in a corresponding mouse carcinogenicity study conducted at the same laboratory. The US EPA has noted that there is no evidence of silver carcinogenicity in humans despite frequent use of therapeutics involving exposures over many years. US EPA has not concluded that silver is carcinogenic.

Interpretation of the carcinogenicity data by KemI appears to be influenced by positive in vitro clastogenicity data. KEMI concludes that there is evidence for clastogenicity in vitro, but is not reassured by the two negative studies of clastogenicity conducted in vivo. Studies of genotoxicity are generally considered more relevant for predicting hazard because in vitro genotoxicity studies typically employ concentrations that cannot be achieved from human exposures. The relevance of the in vivo studies is questioned by KemI on the basis of inadequate evidence of exposure of the target tissue (bone marrow) (see Section 4.1.1, page 30).

Distribution studies confirm the wide distribution of silver to many tissues including blood and bone marrow (Lansdown, 2010; Hadrup and Lam, 2014). Given that silver is systemically distributed to a wide variety of tissues, it is reasonable to assume that silver reached bone via blood circulating through bone marrow. The assertion that the in vivo micronucleus test results, negative for mutagenicity, are invalidated through a lack of target tissue exposure is not supportable by the distribution data. On this basis the demonstrated absence of silver-induced clastogenicity in vivo should be recognised as evidence that insufficient silver can be administered in vivo to induce a clastogenic effect.

The STFNA requests that the classification be reconsidered because the weight of the evidence does not support the conclusion that silver is genotoxic or carcinogenic.

[ECHA note: The following attachment was provided by Silver Task Force North America: Evaluation of Silver Substances under Regulation 528/2012]

Dossier Submitter's Response

According to information on page 45, this attachment is not claimed to be confidential. Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.

In addition, the DS would like to add the following information to some specific statements made above:

The US EPA has evaluated the carcinogenicity study and the assessor concludes (on p 40): "our reviewer believes that these dose-response trends may be linked to treatment and the

use of a higher dose may have better linked the treatment to tumour incidence."(http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-072503_28-Aug-02_006.pdf).
The reason for proposing classification Carc. 2 is because the DS did not consider it safe to disregard the results showing statistically significant positive trends for leukaemia and pituitary adenomas. A trend is a stronger indication of the relevance of an effect and it seems unlikely that this would appear by chance in both sexes (leukaemia).
The absorption of orally administered silver is low (below 5%) thus bone marrow exposure can be expected to be minimal (supported by results from the in vivo genotoxicity study with SZZ). However, the bone marrow is a test system and the absence of mutagenicity due to lack of exposure only means that the test system is inappropriate to use for the substance. It does not prove that SZZ lacks mutagenic potential in tissues exposed to a higher degree (e.g. GI tract, liver). Nevertheless, mutagenicity is a different endpoint and classification category and carcinogenicity is not necessarily linked to this endpoint. There is rather a fear that SZZ acts as a tumour promoter that turns initiated cells into those tumour types the species exposed is prone to develop. In Fischer rats, these include leukaemia and pituitary adenomas whereas humans are more prone to develop other types of tumours.

RAC's response

Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	Germany		MemberState	16

Comment received

The original study report on which the information of Takizawa 1992 is based, is not available to the German CA. However, the DocIII summaries DocIII6.5-05 and -06 provide sufficient detail. In addition, the reliability assessment by the RMS (reliability 2-3) is transparent and appears justified while the reliability assessment by the applicant, which was 2 for the mouse study and 4 for the rat study, remains obscure. Further with regard to the interpretation of the data we fully acknowledge the uncertainties that arise from the use of a rat strain with high spontaneous and variable incidence of mononuclear cell leukaemia (the leukaemia type in Takizawa is not clear from the documentation). According to the RMS there was a statistically significant dose-response relationship. However, we are not sure whether the statistically positive trend might be sufficient for classification for carcinogenicity due to the limited reliability of the results by Takizawa. This should be discussed by RAC. Further information like effects on haematological parameters in repeated dose studies summarised in chapter 4.7.1.1. of the CLH dossier could be taken into account.

Dossier Submitter's Response

Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.

RAC's response

Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	France		MemberState	17

Comment received

The available data on carcinogenicity seem not sufficient to conclude on carcinogenicity classification. Indeed, the study, not GLP, was judged of poor quality (many deficiencies

mentioned by eCA). No general toxicity was observed at the top dose. Moreover, neither leukemia nor pituitary adenomas reach statistical significance. The only indication of the effect was an observed positive trend. Finally, tumours were observed only in rat not in the mouse study in which general toxicity is mentioned.
Dossier Submitter's Response
Please note our general response to comments received on carcinogenicity on the first page of this RCOM table. Compared to statistically significant differences between controls and single dose levels, a trend is a stronger indication of the relevance of an effect since the entire dose-response curve is taken into consideration in such analysis.
RAC's response
Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United States	Fuji Chemical Industries, Ltd.	Company-Manufacturer	18
Comment received				
Inadequate data on causation and dose effects. Inattention to exposure and actual risk. Inappropriate and insufficiently supported extrapolation to a different use (materials protection of polymers for human use as opposed to direct oral ingestion) of data from a different species of silver in different species (genus mus) of animal. Refer to General Comments (above) and to the attached annotated document for further explanation and references. *[ECHA note: The following attachment was provided with the comment above:* Comments on CLH Report: Proposal for Harmonised Classification and Labelling (Swedish Chemicals Agency regarding Silver Zinc Zeolite, April 13, 2015)]				
Dossier Submitter's Response				
Classification is based on the intrinsic properties of the substance and does not take exposure or actual risk into account. Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.				
RAC's response				
Please, see RAC's response to comment number 1. RAC agrees with the DS's response regarding hazard identification under CLP regulation.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Sinanen Zeomic co. Ltd.	Company-Manufacturer	19
Comment received				
For the safety evaluation of SSZ, a 2-year free dietary administration study was conducted, with 3 stages (0.1% to 0.9%) of supplemental doses given to mice and 4 stages (0.01% to 0.3%) of supplemental doses to rats. Neoplastic change in mice showed spontaneous sites and tissue-type but no significant difference was found through statistical methods. Carcinogenicity was therefore denied. With regards to neoplastic change in rats, a dose-dependency was observed in leukemia and pituitary gland tumor, but each incidence rate was within spontaneous frequency of incidence. With regards to non-neoplastic change in				

mice, dose-dependency was observed in islet enlargement in male animals, and renal cyst in both male and female animals. No significant increase was found when comparing the incidence of islet enlargement among 3 administrated groups. No difference in the incidence of renal cyst was identified in any administrated group as well as control groups. With regards to non-neoplastic change in rats, dose-dependency was observed only in hepatobiliary hyperplasia of female rats, but no difference was identified in the incidence among each administrated group including control groups. Incidence of rat leukemia is lower than that of spontaneous leukemia in most of the control groups and the 4 administrated groups. A comparison between control groups and two of the administrated groups (0.01% and 0.03%) shows the incidence is almost the same. Incidence of pituitary gland tumor is lower than that of spontaneous tumor in any of the 4 administrated groups. Data on male rats shows that the incidence is almost the same between control groups and the 4 administrated groups. Data on female rats, when considered by a statistical method, shows no significant difference between control groups and the 4 administrated groups. From the available results, it is correct to conclude that "Carcinogenicity of SZZ is not able to be classified".

[ECHA note: The following confidential attachment was provided with the comment above:] Comments on the proposal for Harmonized Classification and Labelling of Silver Zinc Zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions) according to Regulation (EC) No 1272/2008 (CLP Regulation)

Dossier Submitter's Response

Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.

RAC's response

Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Netherlands		MemberState	20

Comment received

Carcinogenicity
Currently, the evidence for carcinogenicity is not very strong, as also indicated on p70-72. It could be improved with a more thorough discussion on the mechanism of action, especially as the mutagenicity studies were inconclusive.
It is unclear from the current description what type of leukemia was observed. Mononuclear cell leukemia in F344 rats is considered not relevant in humans (http://www.rivm.nl/dsresource?objectid=rivmp:15810&type=org&disposition=inline). If the type of leukemia is unknown, this limits the confidence in the study as this type of information should be available in a study report. In addition, the increase in pituitary adenoma's, which is also a well-known background type of tumour in F344, was only in one sex and not significantly increased compared to controls. Classification in category 2 is therefore doubted.

Dossier Submitter's Response

Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.
Unfortunately, the type of leukaemia is not characterised in the study report and the DS is not aware of any other information that would clarify the mechanism further. As discussed in the CLH report, if SZZ acts as a promoter, the tumour types that the test species is prone to develop would be expected to increase. Humans may not be predisposed to leukaemia

and pituitary adenomas but to other types of tumours that may arise from initiation and promotion of cells into tumour progression.
RAC's response
Please, see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Japanese Society of Industrial Technology for Antimicrobial Articles	Industry or trade association	21
Comment received				
There are no reported adverse health effects associated with silver zinc zeolite that would support the proposed classification. Silver zinc zeolite meets the safety standards established by the Society and the material does not pose a serious health hazard. *[ECHA note: The following attachment was provided with the comment above:* Public Comment Opinion on the Review of Silver Zinc Zeolite underthe European Biocidal Products Regulation]				
Dossier Submitter's Response				
Noted. In the absence of detailed information on factors such as the type of exposure, test substance, exposure levels, number and medical history of exposed population in manufacturers, the statement that no health hazard has been reported cannot be scientifically evaluated and considered in the hazard assessment. Moreover, classification is based on the intrinsic properties of the substance and does not take exposure or actual risk into account. Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.				
RAC's response				
RAC agrees with the DS's response. For comments on carcinogenicity please, see RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Chinese Industry Association for Antimicrobial Materials	Industry or trade association	22
Comment received				
There are no reported adverse health effects associated with silver zinc zeolite that would support the proposed classification. *[ECHA note: The following attachment was provided with the comment above:* Opinion on the Review of Silver Zinc Zeolite under the European Biocidal Products Regulation]				
Dossier Submitter's Response				
Noted. In the absence of detailed information on factors such as the type of exposure, test substance, exposure levels, number and medical history of exposed population in manufacturers, the statement that no health hazard has been reported cannot be				

scientifically evaluated and considered in the hazard assessment. Moreover, classification is based on the intrinsic properties of the substance and does not take exposure or actual risk into account. Please note our general response to comments received on carcinogenicity on the first page of this RCOM table.
RAC's response
Please see RAC's response to comment number 21.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Japanese Society of Industrial Technology for Antimicrobial Articles	Industry or trade association	23
Comment received				
There are no reported adverse health effects associated with silver zinc zeolite that would support the proposed classification. Silver zinc zeolite meets the safety standards established by the Society and the material does not pose a serious health hazard. *[ECHA note: The following attachment was provided with the comment above:* Public Comment Opinion on the Review of Silver Zinc Zeolite underthe European Biocidal Products Regulation]				
Dossier Submitter's Response				
Noted. In the absence of detailed information on factors such as the type of exposure, test substance, exposure levels, number and medical history of exposed population in manufacturers, the statement that no health hazard has been reported cannot be scientifically evaluated and considered in the hazard assessment. Moreover, classification is based on the intrinsic properties of the substance and does not take exposure or actual risk into account.				
RAC's response				
RAC agrees with the response of the DS.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Chinese Industry Association for Antimicrobial Materials	Industry or trade association	24
Comment received				
There are no reported adverse health effects associated with silver zinc zeolite that would support the proposed classification. *[ECHA note: The following attachment was provided with the comment above:* Opinion on the Review of Silver Zinc Zeolite under the European Biocidal Products Regulation]				
Dossier Submitter's Response				
Noted. In the absence of detailed information on factors such as the type of exposure, test substance, exposure levels, number and medical history of exposed population in manufacturers, the statement that no health hazard has been reported cannot be				

scientifically evaluated and considered in the hazard assessment. Moreover, classification is based on the intrinsic properties of the substance and does not take exposure or actual risk into account.
RAC's response
RAC agrees with the DS's response. Moreover, neither the DS nor RAC is proposing classification for mutagenicity.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	Germany		MemberState	25
Comment received				
With regard to the discussion on bone marrow genotoxicity and distribution of the silver to this tissue, we would like to note that silver is considered to form deposits / pigmentation / discoloration in tissues over time (as described in CLH report chapters 4.7.1.1-4.7.,1.5). Notably, the available in vivo genotoxicity study was using single application. This may not have been adequate to reflect silver tissue distribution / accumulation as described for repeated exposure. We agree that an in vivo comet assay on relevant target tissues as discussed in the CLH dossier might be the most appropriate choice for further testing.				
Dossier Submitter's Response				
Agree				
RAC's response				
RAC agress with comment from the MSCA.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Sinanen Zeomic co. Ltd.	Company-Manufacturer	26
Comment received				
SZZ was authorized for use as "Zinc, ammonia, silver complex substitution type zeolite" and notified in the official gazette by the Ministry of Health, Labour and Welfare No. 331 of 2014. Since then, about 50 companies have adopted it for use in the commercialization of their own products. At the time of approval, safety data of SZZ was submitted to the authority. The substance was concluded negative for mutagenicity. *[ECHA note: The following confidential attachment was provided with the comment above:]* Comments on the proposal for Harmonized Classification and Labelling of Silver Zinc Zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions) according to Regulation (EC) No 1272/2008 (CLP Regulation)				
Dossier Submitter's Response				
In the absence of further information on the data upon which the conclusion "negative for mutagenicity" is made, the attachment is not considered to add any information of relevance for the decision whether or not it is possible to classify SZZ for genotoxicity.				
RAC's response				
RAC agrees with the response of the DS.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Belgium	Precious Metals & Rhenium consortium c/o European Precious Metals Federation	Industry or trade association	27

Comment received

- Hazard classification of SZZ for developmental toxicity based on read-across from effects observed in studies with inorganic "silver" is not justified, since the observed effects are secondary to non-specific disruption of maternal homeostasis.

- Oral exposure of rats to high doses of an inorganic silver substance (silver acetate) inadvertently causes a massive shift in intestinal microbiota – this is correlated with the (otherwise desired) antimicrobial efficacy of silver; especially several enterobacterial sub-populations are diminished, resulting in severe gastroenteritis and thus contributing to a general disruption of homeostasis with an impairment of ETE metabolism on a broad scale (not restricted to copper alone) in the intestinal tract.

- In addition to the above, embryotoxic effects of silver chloride were experienced in rats during dietary administration of a very high dose of 188 mg Ag/kg bw during the entire period of gestation (Shavlovski et al., 1995); however, this must not be considered a direct effect of silver ions on embryogenesis, but instead represent a "secondary non-specific consequence" of the disruption of systemic copper homeostasis in dams resulting in copper deficiency. The reasoning for this is that disturbed copper homeostasis in dams is accompanied by the formation of a silver-modified, functionally inactive ceruloplasmin lacking copper transport function. Thereby, the availability of copper to the fetus is reduced because plasma ceruloplasmin is the main source of copper for placenta and fetus. Overall, this secondary trace element deficiency in offspring does not constitute evidence for specific developmental toxicity of silver ions.

- Comparing the findings of oral repeated dose toxicity studies of the silver-substituted zeolites SZZ and "silver containing active substance 2" as well as of unmodified zeolite A, it becomes obvious that the histopathological effects which determine the NOAELs from these studies originate from the non-substituted (unmodified) zeolite moiety itself, and that the modification of zeolite with silver does not have any appreciable influence on the toxicological effects.

- Overall, based on the available mechanistic information and the considerations given in the CLP guidance with respect to classification for developmental toxicity in the presence of maternal toxicity through "secondary non-specific mechanisms" related to the disruption of maternal homeostasis, it is not considered justified to use the Shavlovski data on silver chloride (1995) in support of classification of silver substances for developmental toxicity Category 1B or Category 2.

For further details / justification, please refer to the attached document, pages 14-27.

[ECHA note: The following attachment was provided with the comment above:
Comments on the Proposal for Harmonised Classification and Labelling for Silver zinc zeolite By the Precious Metals and Rhenium Consortium (PMC)]

Dossier Submitter's Response

• Please note that the classification proposal for reproductive toxicity is based on data on silver zinc zeolite. The published study with silver chloride is considered as supporting information providing further information on a plausible mechanism.
• According to the publication referred to, silver acetate had, in gene expression studies, an effect on the representative bacterial population in ileum. However, potential effects of this was not studied and the authors conclude "the potential health effects of these observed changes are unknown and should be investigated further". Gastroenteritis was considered the cause of death of rats in this published study however this was not an effect observed among the rodent studies with silver zinc zeolite (vomiting occurred in dogs). Therefore, we do not see how this information should be taken into consideration in this context.
• Please note that this classification entry covers certain types of silver zinc zeolites. The classification proposals made for the human health hazard classes are thus based on substance-specific information on the intrinsic hazards of the substance, not of its constituents. Therefore, in this respect it is less relevant if effects are due to the presence of silver, zinc, zeolite or other components of the substance. Nevertheless, for transparency and for comparison of effects, data on other silver substances are included and discussed in the CLH report where relevant but read across has not been applied.
•We agree that there is a substantial amount of data demonstrating that silver can displace copper in enzymes resulting in a copper deficiency in foetuses. However, it is not known whether or not this is the only mechanism for the foetal toxicity observed. Nevertheless, this specific mechanism of silver results in severe developmental effects regardless if silver has a direct or indirect effect.

RAC's response

RAC agrees with the DS's response. Please see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Netherlands	TNO	National NGO	28

Comment received

No classification is proposed for effects on fertility as no effects on reproductive function or other related effects were observed.
The minimal effects seen in the pups of the low dose group should not be considered as developmental effects but only as toxicity effect caused by copper depletion and furthermore it should be noted that the effect is not more severe in the F2 pups when compared to the F1 pups. At this dose level also minimal maternal toxicity was observed.
The effects at higher doses were in accordance with effects seen in reproductive studies with copper depletion and were seen in the presence of mortality and severe maternal toxicity.
In addition, the effects in the prenatal developmental studies with other silver containing active substances occur in the presence of maternal toxicity; effects in dams and pups were observed at the same concentration. Furthermore, the effects

observed in the two-generation reproductive toxicity study are most probably caused by a depletion of copper and can be considered to be a toxic effect rather than a developmental effect and therefore this compound should not be classified. For detailed justification, please see attached confidental document.

[ECHA note: The following confidential attachments were provided with the comment above:] TNO Comment on carcinogenicity of Silver Zinc Zeolite and TNO Comment on reproductive toxicology of silver zinc zeolite.

Dossier Submitter's Response

Please note that TNO is acting as consultant company for one of the companies participating in the silver task force.
High dose pups were severely affected by treatment and were either found dead or died within a few days after delivery. The same effects were seen but to less extent at the mid dose level. As discussed in the CLH report and in our general response to comments on reproductive toxicity, these effects occurred in the absence of maternal mortality and severe maternal toxicity. The assessment is complicated by high dose pups failing to survive and become parents.
We agree that there is a substantial amount of data demonstrating that silver can displace copper in enzymes resulting in a copper deficiency in foetuses. However, it is not known whether or not this is the only mechanism for the foetal toxicity observed. Nevertheless, this specific mechanism of silver results in severe developmental effects regardless if silver has a direct or indirect effect. This is further discussed in our general response on the first page of this RCOM.

RAC's response

RAC agrees with the DS's response. Please see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2015	United Kingdom	European BPR Silver Task Force	Industry or trade association	29

Comment received

Reproductive Toxicity - CLH Report Section 4.10, page 73 to 91
The eCA proposes reproductive hazard classification for silver zinc zeolite (Category 1B, H360D).
The classification for reproductive toxicity in Category 1B (H360d) is based on offspring mortality in the two-generation toxicity study performed with silver zinc zeolite.
The effects of silver zinc zeolite on foetal and neonatal viability are seen in this study at dose levels sufficient to cause marked parental toxicity. Effects on F1 offspring were seen at 12500 ppm, a dose level sufficient to cause parental mortality. Effects on F2 offspring were seen at 6250 ppm, the highest dose level investigated in this generation and which was sufficient to cause a high level of parental mortality.
The effects can be attributed to microcytic anemia due to an induced copper deficiency. The haematological effects are more clearly identified in a 90-day rat study with silver zinc zeolite which used the same strain of rat and the same dose levels as the reproduction study. The mid- and high dose levels in the 90-day study were associated with decreased haemoglobin, decreased mean corpuscular volume and decreased mean corpuscular haemoglobin. This type of anemia is characteristic of excessive dietary exposure to zinc. Haematological effects of excessive zinc exposure are well-known and have been described in the scientific literature. The mid-dose level of 6250 ppm in the 90-day study is equal to 82.45 mg/kg/day of zinc and this is well above the dose level of zinc that is associated with toxicity. Haematological effects are only seen in studies of silver zinc zeolite and not in

studies with other forms of silver zeolite or with silver salts.
The effects may also be attributed to disturbed parental copper homeostasis by the formation of a silver-modified, functionally inactive ceruloplasmin lacking copper transport function. The availability of copper to the foetus is therefore reduced because plasma ceruloplasmin is the main source of copper for placenta and foetus. This secondary trace element deficiency in offspring does not constitute evidence for specific developmental toxicity of silver ions.
Overall, based on the available mechanistic information and the considerations given in the CLP guidance with respect to classification for developmental toxicity in the presence of maternal toxicity through "secondary non-specific mechanisms" related to the disruption of maternal homeostasis, it is not considered justified classify silver zinc zeolite for developmental toxicity Category 1B or Category 2.

[ECHA note: The following confidential attachments were provided with the comment above:]

- EU Silver Task Force expert opinion on the carcinocenicity and reproductive toxicity potential of silver and AEL derivation
- Reproductive Toxicology of Silver Zinc Zeolite
- Carcinogenic and Teratogenic Potential of Silver Zinc Zeolite
- Evaluation of a two-generation study with silver zinc zeolite
- Reproductive and developmental toxicity of siver zinc zeolite

Dossier Submitter's Response

Please note our general response on the first page of this rCOM document.

RAC's response

RAC agrees with the DS's response. Please see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2015	United States	Silver Task Force North America	Industry or trade association	30

Comment received

Reproductive toxicity is identified by KEMI in a study of silver zinc zeolite, a developmental study of silver acetate and a developmental study of silver chloride. The mid- and high dose levels of the study of silver zinc zeolite were characterized by parental toxicity which indicated excessive dosing and zinc, rather than silver, toxicity. Developmental effects in this study were clearly secondary to parental toxicity. The authors of this US National Toxicology Program study, subjected to extensive peer review, concluded that the study showed "the absence of any statistically or biologically significant developmental toxicity". The third study cited as support for classification, only showed evidence of developmental toxicity at the sole dose level of 250 mg/kg/day. The extent of maternal toxicity is unknown in this study. The Silver Task Force of North America recommends that weight of the evidence for reproductive toxicity be revisited for purposes of classification. While reproductive effects seen in the two-generation study were not associated with marked mortality or severe bodyweight effects in parental animals, data show an association with anaemia in the reproduction study and a subchronic study conducted at the same dose levels. Mechanistic data indicate that the anemia and reproductive effects are due to an induced copper deficiency due to excessive zinc intake in parents and the reproductive effects are therefore secondary to systemic toxicity.

[ECHA note: The following attachment was provided by Silver Task Force North America: Evaluation of Silver Substances under Regulation 528/2012]

Dossier Submitter's Response
According to information on page 45, this attachment is not claimed to be confidential. Please note that the classification proposal for reproductive toxicity is based on data on silver zinc zeolite. The published study with silver chloride is considered as supporting information providing further information on a plausible mechanism. We agree that there is a substantial amount of data demonstrating that silver can displace copper in enzymes resulting in a copper deficiency in foetuses. However, it is not known whether or not this is the only mechanism for the foetal toxicity observed. Nevertheless, this specific mechanism of silver results in severe developmental effects regardless if silver has a direct or indirect effect. This is further discussed in our general response to comments received on reproductive toxicity on the first page of this document.
RAC's response
RAC agrees with the DS's response. Please see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	Germany		MemberState	31
Comment received				
The proposed classification for reproductive toxicity in Category 1B (H360D) is based on pup mortality (mainly PND 1-4) seen at the highest dose (12500ppm) in the two-generation reproductive toxicity study in rats. However, from our point of view the proposed classification might be questionable. The following issues should be considered to decide on classification: 1. Parental toxicity was observed at 12500ppm e.g. mortality, macroscopic and microscopic changes in kidney as well as changes in haematology parameters. It should be mentioned, that the systemic toxicity in females is less pronounced than in males. Moreover, in F1 young a high mortality rate was observed in females (77 %) at 12500ppm. In these animals e.g. histopathological damage was noted in the kidneys. This finding supports that 12500ppm represents a dose maternally toxic in the dams of the parental generation. In addition, in the mid dose no effects on pup survival were observed, which leads to a questionable dose-response relationship. In our opinion it should be discussed, whether the reduced postnatal survival might be due to a lack of maternal care as a result of severe maternal toxicity. 2. The discussion of the role of zinc in reproductive toxicity of silver zinc zeolite is missing and the relevance of zinc toxicity should be discussed in the CLH dossier for the following reasons: After repeated administration of zinc in animal studies kindneys are one of the main target organs for toxic effects. Zinc is also associated with the induction of anaemia. A chronic excess of zinc in the diet can result in a disturbance of copper availability. As consequence of copper deficiency a disturbance in iron utilization can occur which can result in anaemia. Therefore, the observed parental toxicity could be zinc-associated toxicity. Furthermore, indications of similar postnatal developmental toxicity (e.g. decreased number of live offspring and decreased survival to PND4) were found in a two-generation study with zinc chloride in rats (Khan et al. 2007) at maternally toxic dose levels (MAK, 2010). 3. The embryotoxic potential of silver is discussed based on only one research publication (Shavlovski et al., 1995). The proposed mechanism of silver toxicity is a decrease of active ceruloplasmin from blood and consequently a reduced availability of copper. In this publication maternal toxicity was not described. In developmental toxicity studies performed				

with other silver containing substances described in the CLH dossier no similar effects occurred. From our point of view zinc toxicity could be more relevant than the proposed silver toxicity.

References:
MAK Value Documentation, 2010 – Zinc and ist inorganic compunds (available at: http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics)

Khan AT, Graham TC, Ogden L, Ali S, Thompson SJ, Shireen KF, Mahboob M (2007) A two generational reproductive toxicity study of zinc in rats. J Environ Sci Health B 42: 403–415

Dossier Submitter's Response

Please note our general response to comments received on reproductive toxicity. However, the DS would like to add the following comments to the points above:

1. The less pronounced toxicity in high dose P/F0 females is discussed in section 4.10.5. The high mortality in F1 females is, in our view, a consequence of the poor condition of pups surviving delivery. These animals never became parents. However, as discussed in the report, there was no mortality in high dose P/F0 thus we do not see that maternal toxicity would explain developmental toxicity in pups. The stillborn index in 6250 ppm F1 pups was increased but statistical significance was not achieved (2.6% compared to 0.8% in controls). However the increased stillborn index in 6250 ppm F2 pups was statistically significant (5.4% compared to 1.1% in controls). Maternal neglect is discussed in the CLH report on page 90: *"A reduced food intake was observed in high dose females compared to controls during lactation. However, there were no abnormalities detected in any of the high dose dams during the clinical observations made during lactation. Considering that many of the dams lost some of their pups during the first days, the reduced food intake could solely illustrate the food demand being lower due to less lactating pups. The effects seen in pups (i.e. reduced number of pups, reduced livebirth/increased stillborn index, reduced bodyweight gain, reduced pup survival indices, clinical signs (pale), histopathological changes in kidneys, heart, liver and reduced thymus) can thus not be considered being due to maternal neglect. "*

2. We agree that zinc may contribute to effects observed with szz. However this is an element present in the substance and the classification proposals are made for the substance SZZ. If read across is applied between different silver substances it may be important, if possible, to identify effects caused by each constituent of the substance but we do not see that it is relevant in this case.

3. The classification proposal is based on severe effects observed in the guideline study with SZZ. The published study on silver chloride is used as supporting data providing information on a plausible mechanism. As discussed in the CLH report and in our general response, the lack of effects with other silver containing substances may be due to

a. effects of silver manifest above a critical silver exposure level and the exposure to silver in other developmental toxicity studies (based on silver content and release) is lower than in the study with SZZ and/or
b. silver and zinc share the same mechanism for developmental toxicity. Therefore, due to the presence of zinc in SZZ, the critical level where effects manifest is exceeded even though the silver exposure seems to be similar in the fertility studies with SZZ and a different silver containing substance,
c. the exposure duration is too short to completely inactivate ceruloplasmin in the blood.

Shavlovski and co-workers demonstrated that effects were only observed if exposure was continuous during the entire gestation period (days 1-20). When restricted to days 7-15, effects were not observed. The exposure period in the developmental studies performed with other silver containing substances was between days 6 and day 15 (or 19 in one study) d. copper is present in at least one of the other silver containing substances. This may be sufficient to counteract effects of silver (and perhaps zinc) by keeping the copper level in excess of silver (and perhaps zinc) and thus preventing other metals from binding to ceruloplasmin.
RAC's response
RAC agrees with the DS's response. Please see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United States	Fuji Chemical Industries, Ltd.	Company-Manufacturer	32
Comment received				
Inadequate data on causation and dose effects. Inattention to exposure and actual risk. Inappropriate and insufficiently supported extrapolation to a different use (materials protection of polymers for human use as opposed to direct oral ingestion) of data from a different species of silver in different species (genus mus) of animal. Refer to General Comments (above) and to the attached annotated document for further explanation and references. *[ECHA note: The following attachment was provided with the comment above:* Comments on CLH Report: Proposal for Harmonised Classification and Labelling (Swedish Chemicals Agency regarding Silver Zinc Zeolite, April 13, 2015)]				
Dossier Submitter's Response				
Classification is based on the intrinsic properties of the substance and does not take exposure or actual risk into account. Please note our general response to comments received on reproductive toxicity on the first page of this RCOM.				
RAC's response				
RAC agrees with the DS's response. Please see RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Sinanen Zeomic co. Ltd.	Company-Manufacturer	33
Comment received				
Two-generation reproductive toxicity study using rats provides test data on SZZ. SZZ was administered in the diet to rats. Additive concentrations were 1,000, 6,250 and 12,500 ppm. The NOEL (no observed effect level) for reproductive toxicity and filial toxicity in the two-generation test is 1,000ppm. No adverse effect on reproductive function was found, and the adverse effect observed in filial rats is entirely attributed to secondary effects of maternal toxicity. The literature studies considered include analytical data on the silver and copper component in rat blood plasma after intraperitoneal rapid intravenous administration of silver chloride. A description in the report suggests that, by administration of silver, iron and copper component having disturbed homeostasis can lead to copper abstraction effect and that this is the reproductive toxicity mechanism of silver. The mechanism results in				

indirect toxicity to filial rats since maternal toxicity (copper deficiency) must occur first. It is noted that use of SZZ in antimicrobial applications provides very small amounts of SZZ that cannot replicate the effects seen in any of the studies used to establish classification.

[ECHA note: The following confidential attachment was provided with the comment above:] Comments on the proposal for Harmonized Classification and Labelling of Silver Zinc Zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions) according to Regulation (EC) No 1272/2008 (CLP Regulation)

Dossier Submitter's Response

The DS agrees that there is a substantial amount of data indicating that silver can displace copper in enzymes resulting in a copper deficiency in foetuses. However, it is not known whether or not this is the only mechanism for the foetal toxicity observed in the study with SZZ. Moreover, it is not known if there is a copper deficiency in dams and it is not known if the sensitivity of pups in that case is higher. Regardless of whether or not silver causes direct or indirect effects, data show that exposure to SZZ results in severe developmental toxicity. This is further discussed in our general response to comments received on reproductive toxicity.
Classification is based on the intrinsic properties of a substance and does not take exposure and risk into consideration.

RAC's response

RAC agrees with the DS's response. Please see RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Netherlands		MemberState	34

Comment received

Reproductive toxicity
We agree that Ag Zn zeolite should be classified for effects on development as observed in the 2-generation study. However, some further discussion is needed concerning the type of observed effects warranting which classification and the possibility of the effects being secondary to maternal toxicity. The increase in prenatal mortality was only observed at the highest dose in the F1 generation and at the mid dose in the F2 generation (F2 high dose not tested). The P-generation at the high dose showed a clear reduction in Hb concentration (which could be caused by reduced Cu or Fe uptake) indicating that the pre-natal mortality could be secondary to reduced oxygen supply to the fetus. This could be considered as secondary to marked unspecific toxicity as all type of cells are affected by a lack of oxygen. However, the lack of Hb could also occur in the fetus for the same reasons and resulting in pre-natal mortality. This would be considered a specific effect on the fetus. As Hb was not determined in the parental F1 animals it is also unclear whether the same pre-natal effects could be secondary to maternal anemia. The developmental studies with silver compounds show only pre-natal mortality when the exposure is continued until day 19 or 20 but not when stopped at day 15. This shows that the effects are either caused by a continuously reduced uptake of Cu (or Fe) or that the reduced maternal or fetal Hb is only relevant at the last days of gestation. However, the absence of comparable effects in the 2-generation with another silver compound at estimated Ag levels above those in the study with Ag Zn zeolite is not consistent. Is there an explanation?

It is also stated that according to the repeated dose study report zinc prevents uptake of copper in the GI tract, which suppresses production of ceruloplasmin. Please provide information whether soluble zinc compounds induce comparable developmental effects.

The increased post-natal mortality in the study with Ag Zn zeolite could be either due to the pre-natal exposure but also to the reduced presence of Cu (or Fe) in the milk. The last is suggested by the observation that there were no treatment related histopathology findings in stillborn and day 4 culled pups, but anemia like clinical effects in pre-weaning and histopathological effects in day 26 pups. However, the occurrence of post-natal mortality in the study by Zhavlovski suggests that this could be due to pre-natal exposure. Maybe both classifications (developmental and lactation) should be considered. In the summary table (p73), the unit of the dose (ppm) is not given in the results column. This is confusing, as the dose is depicted in mg/kg bw/day in the method column. On page 75, the reference to 4.11.5 should be to 4.10.5. Similarly, on page 77 last sentence, the reference should be to 4.10.3 instead of 4.11.3.
Dossier Submitter's Response
The reason why less effects were observed in the fertility study with a different silver containing substance is assumed to be due to the presence of zinc in SZZ which is assumed to have the same ability to displace copper in ceruloplasmin as silver. Zinc is not present in the other silver containing substance. Therefore, even if the exposure to silver is similar between SZZ and the other silver containing substance, the presence of Zn in SZZ adds to the effect and the two metals is expected to be in excess of copper. According to information in the risk assessment report for zinc chloride (prepared by the Netherlands Organisation for Applied Scientific Research (TNO) and the National Institute for Public Health and the Environment (RIVM)), ceruloplasmin activity and plasma copper levels are used as indicators of the copper status in humans. Studies seem to indicate that intake of zinc reduces serum ceruloplasmin levels with a higher sensitivity of women. However, since this entry considers SZZ, a substance in which zinc is a constituent, it is not considered crucial for classification of the substance to know if effects are caused by silver, zinc or other components of the substance. The statement referred to from the repeated dose toxicity study report, i.e. zinc prevents copper uptake and thus suppresses ceruloplasmin in the GI tract, is a statement from the study author and is included for transparency in the discussion on a potential mechanism of SZZ toxicity. The line of reasoning is very interesting but based on the data available, the DS finds it difficult to compare and conclude on effects in dams and pups. Besides the fairly crude measurements of F2 pup homogenates, there is no data on the levels of copper, silver, zinc or iron in parental animals or pups. Therefore, it is not possible to assess if there is a copper deficiency also in the parents and/or if the copper deficiency is more pronounced in the pups. Nevertheless, since dams show no treatment-related clinical signs whereas pups clearly fail to survive, the sensitivity of pups seems indeed to be much higher. Likewise, if effects in the pups are due to an iron deficiency caused by silver and/or iron that is also affecting the dams, pups are obviously unable to cope with this. We agree that classification for lactation could be considered. Pale organs were indeed observed in day 21 pups but at this age, pups have been eating diet for up to a week thus it is difficult to conclude that effects arise during the lactation period. We are grateful for the corrections proposed and apologize for these mistakes.
RAC's response
RAC agrees with the DS's opinion. Please see RAC's response to comment number 1.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILVER ZINC ZEOLITE (ZEOLITE, LTA FRAMEWORK TYPE, SURFACE MODIFIED WITH SILVER AND ZINC IONS)

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Japanese Society of Industrial Technology for Antimicrobial Articles	Industry or trade association	35
Comment received				
There are no reported adverse health effects associated with silver zinc zeolite that would support the proposed classification. Silver zinc zeolite meets the safety standards established by the Society and the material does not pose a serious health hazard. *[ECHA note: The following attachment was provided with the comment above:* Public Comment Opinion on the Review of Silver Zinc Zeolite underthe European Biocidal Products Regulation]				
Dossier Submitter's Response				
In the absence of further information on exposure situations (exposure levels, exposure route, number of exposed individuals etc), this information cannot be scientifically assessed. Moreover, classification is based on the intrinsic properties of a substance and does not take exposure and risk into consideration.				
RAC's response				
RAC agrees with the DS's response. Please see RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Chinese Industry Association for Antimicrobial Materials	Industry or trade association	36
Comment received				
There are no reported adverse health effects associated with silver zinc zeolite that would support the proposed classification. *[ECHA note: The following attachment was provided with the comment above:* Opinion on the Review of Silver Zinc Zeolite underthe European Biocidal Products Regulation]				
Dossier Submitter's Response				
In the absence of further information on exposure situations (exposure levels, exposure route, number of exposed individuals etc), this information cannot be scientifically assessed. Moreover, classification is based on the intrinsic properties of a substance and does not take exposure and risk into consideration.				
RAC's response				
RAC agrees with the DS's response. Please see RAC's response to comment number 1.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Netherlands		MemberState	37
Comment received				

Skin irritation/corrosion: As scar formation was observed in 1 out of 6 rabbits and scar formation is considered sufficient evidence for corrosivity especially in combination with scab formation, classification as corrosive could be considered. The differences in response between the different zeolites could also be caused by differences in Ag and/or Zn content and release under watery conditions. This would indicate that different classifications would be applicable to the different substances. Please provide argumentation why for these local effects the different Ag Zn zeolites are expected to have the same properties. This difference is further substantiated by the results of the eye irritation study, which shows that the same zeolite form has clearly different properties than the other forms, which cannot be caused by a difference in solvent.
Dossier Submitter's Response
The DS agrees that classification as corrosive could be considered. This is discussed on page 40 of the CLH report. The reason for proposing Skin Irrit rather Skin Corr is because crust formation is not considered to meet the definition of a scar and the latter was only observed in 1/6 animals (criteria states 1/3). Variations between results from different irritation studies are not uncommon even when performed with a single substance. To our knowledge, this usually does not prevent taking a decision on classification.
RAC's response
RAC agrees with the DS's response.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Sinanen Zeomic co. Ltd.	Company-Manufacturer	38
Comment received				
SZZ was authorized for use as "Zinc, ammonia, silver complex substitution type zeolite" and notified in the official gazette by the Ministry of Health, Labour and Welfare No. 331 of 2014. Since then, about 50 companies have adopted it for use in the commercialization of their own products. At the time of approval, safety data of SZZ was submitted to the authority. The substance was concluded negative for irritation effects. *[ECHA note: The following confidential attachment was provided with the comment above:]* Comments on the proposal for Harmonized Classification and Labelling of Silver Zinc Zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions) according to Regulation (EC) No 1272/2008 (CLP Regulation)				
Dossier Submitter's Response				
The reference (http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000032704.pdf) only informs that the substance is restricted for use in certain cosmetics (and states the maximum concentration allowed). There is no information on toxicological test data thus the statement "negative" in a skin primary irritation test for rabbits cannot be verified.				
RAC's response				
RAC agrees with the DS's response.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	Sinanen Zeomic co. Ltd.	Company-Manufacturer	39
Comment received				
SZZ was authorized for use as "Zinc, ammonia, silver complex substitution type zeolite" and notified in the official gazette by the Ministry of Health, Labour and Welfare No. 331 of 2014. Since then, about 50 companies have adopted it for use in the commercialization of their own products. At the time of approval, safety data of SZZ was submitted to the authority. The substance was concluded negative for sensitisation effects. *[ECHA note: The following confidential attachment was provided with the comment above:]* Comments on the proposal for Harmonized Classification and Labelling of Silver Zinc Zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions) according to Regulation (EC) No 1272/2008 (CLP Regulation)				
Dossier Submitter's Response				
The reference (http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000032704.pdf) only informs that the substance is restricted for use in certain cosmetics (and states the maximum concentration allowed). There is no information on the toxicological test data thus the statement "negative" in a skin sensitization test cannot be verified.				
RAC's response				
RAC agrees with the DS's response.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Belgium	Precious Metals & Rhenium consortium c/o European Precious Metals Federation	Industry or trade association	40
Comment received				
- The repeated dose toxicity studies on silver and/or zinc modified zeolites summarised in the repeated dose toxicity section of the CLH report cover some consistent treatment-related effects, including histopathological changes in the kidneys. Adverse effects in the kidneys and urinary bladder have been consistently reported in repeated dose studies with non-substituted zeolite A. In particular, deposition of crystalline material in the kidney and the excretion of this material via the urine may cause mechanical damage in the kidney and bladder associated with epithelial hyperplasia in these organs. Based on the toxicity study dataset available for simple silver substances, the kidney does not appear to be a target organ. Hence, there is a good basis to conclude that the renal changes, including hydronephrosis, observed with silver zinc zeolite can be attributed to the zeolite moiety. - The pattern of tissue pigmentation observed in the various repeat dose toxicity studies following treatment with SZZ is consistent with the deposition of insoluble				

silver complexes. In relation to the CLP endpoint criteria, a robust basis for the assignment of a STOT-RE classification in respect of this phenomenon is lacking, as it was not clearly correlated with significant attendant toxicity in terms of pathological or functional change. The weight of evidence from the historical database of investigations on such tissue-associated silver precipitates (see for example Landsdown, 2010) which includes mechanistic studies of argyria, indicates that such deposits are inert and not associated with pathological damage.

For further details / justification, please refer to the attached document, pages 10-12.
[ECHA note: The following attachment was provided with the comment above:
Comments on the Proposal for Harmonised Classification and Labelling for Silver zinc zeolite By the Precious Metals and Rhenium Consortium (PMC)]

Dossier Submitter's Response

This classification entry covers specific types of silver zinc zeolites hence the classifications proposed for the human health hazard classes are based on the intrinsic hazards identified in toxicological studies for this type of substance and not on the individual constituents. Therefore, in this respect, it is less relevant if kidney effects are due to the presence of silver, zinc, zeolite or other components of the substance. However, it is not possible to exclude from existing data that accumulation of a heavy metal in organs and tissues could be related to the systemic effects observed, including kidney effects. The DS considers this irreversible effect to be an undesired effect that should be avoided.

RAC's response

RAC agress with the comment. RAC does not consider hyperpigmentation a sufficiently severe adverse effect and therefore proposes no classification for STOT RE.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Netherlands		MemberState	41

Comment received

STOT RE: In the conclusion on STOT RE on p60 it is stated that 'Based on the pigmentation and the hydronephrosis observed at the lowest dose level in the two-generation study, classification STOT RE 2; H373 is proposed.' However, in the comparison of nephrotoxicity with the guidelines (p59), no conclusion is reached. A comparable effect is only detected in the repeated dose studies at dose levels clearly above the guidance value. This could be stated more clearly, or the conclusion should be adapted. Moreover, considering pigmentation is not a true adverse effect, and only occurs in one study below the guideline value, it is doubtful this effect on its own provides sufficient basis for classification.

Dossier Submitter's Response

The proposal stated in section 4.7.2 is based on the nephrotoxicity (and pigmentation) observed in several species that in the rat occurred at doses close to the guidance value range. Consequently the conclusion is that although the LOAEL for nephrotoxicity cannot be set (effects were seen at the lowest dose level) and it is thus not known if effects occur within the guidance value range, criteria are considered fulfilled since values are intended for guidance, not as demarcation values.
In our view, it is not possible to exclude from existing data that accumulation of a heavy metal in organs and tissues could be related to the systemic effects observed. Therefore, this irreversible and undesired effect should be avoided. Pigmentation was considered the critical effect for the LOAEL/NOAEL set for sodium silver thiosulfate under 1107/200 (for which the NL was the rapporteur) and the basis for the classification proposed in the DAR (R33 which translates into STOT-RE). See EFSA Journal 2013;11(10):3136.

RAC's response
RAC agrees with the comment. RAC does not consider hyperpigmentation a sufficientlty severe adverse effect and therefore proposes no classification for STOT RE.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	Germany		MemberState	42
Comment received				
Irreversible pigmentation / discoloration by silver deposition is well documented and should warrant classification as STOT RE 2.				
Dossier Submitter's Response				
Agree.				
RAC's response				
RAC disagrees with the comment. RAC does not consider hyperpigmentation a sufficiently severe adverse effect and therefore proposes no classification for STOT RE.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Belgium	Precious Metals & Rhenium consortium c/o European Precious Metals Federation	Industry or trade association	43
Comment received				
Our comments on the environmental hazard assessment are mainly related to the use of inadequate methodology for inorganic substances: - The Unit World Model (UWM) is introduced and the rapid removal of silver from the water column. - It is suggested to use the ecotoxicity reference values from the silver and zinc REACH registration files. - It is suggested to apply the M-factor rules in line with the CLP guidance on metals and to perform Transformation / Dissolution testing. For further details / justification, please refer to the attached document, pages 28-33. *[ECHA note: The following attachment was provided with the comment above:* Comments on the Proposal for Harmonised Classification and Labelling for Silver zinc zeolite By the Precious Metals and Rhenium Consortium (PMC)]				
Dossier Submitter's Response				
The Transformation / Dissolution test was not necessary for the environmental risk assessment of silver zinc zeolite and was, therefore, not required. Classification issues were explicitly not dealt with at technical meeting for biocides. It is the responsibility of the applicant for the active substance to provide the necessary information. Silver ions react quickly with sulfidic compounds and adsorb to particulate organic matter. However, this does not imply the substance is not available to animals. Particle feeders may take up the particle bound silver via food. Studies have shown that silver can be re-dissolved in the stomach, even sulfidic silver. We have discussed this in chapter 5.3 and the				

provided literature reviews.
RAC's response
Noted. Please see the RAC opinion for more details.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2015	Netherlands		MemberState	44

Comment received

Comment 1
In principle, we can agree with the conclusion that BCF is not applicable for silver zinc zeolite but the arguments used in the report for bioaccumulation are not well-founded. For bioconcentration and bioaccumulation it is stated that "it is unlikely that this insoluble high molecular weight compound is passing biological membranes" and "the compound itself is likely not passing into the body". Nevertheless, the substance is proposed to be Repr. 1B on the basis of a dietary rat study. In this study, systemic effects were observed. If this would be caused by the silver zinc zeolite, this suggests at least some uptake of the compound (or one more of its constituents, i.e. silver, zinc or zeolite). Please explain.

Comment 2
In 2012, the RIVM in the Netherlands has published a report on the derivation of ecological risk limits for silver (Moermond and van Herwijnen, RIVM report number 601714023; available at http://www.rivm.nl/bibliotheek/rapporten/601714023.html). In this report many more endpoints considered reliable are presented originating from public studies and the public REACH database for registered substances. This concerns data for additional species and taxonomic groups. These studies and additional studies published after 2010 should be assessed for the purpose of classification and labeling and included in the report. Although NL does agree that this is unlikely to influence the classification, it might result in amended M-factors. Please indicate if these additional studies would influence the classification.

Comment 3
For the uses it is stated that silver zinc zeolite is incorporated into polymers, compounded into coatings or applied topically onto materials. In section 5.4 on aquatic toxicity (p. 100) it is stated that the zeolite part is likely to remain in the polymer matrix. This is in contradiction with its topically application and the statement should be considered invalid. The presented ecotoxicity data on the silver zinc zeolite, however, indicate that the substance itself is less toxic than the silver released and this clearly supports the classification being based on silver.

Comment 4
In section, 5.5.1.1 LC50 values are referred to as NOEC, this is confusing and it should be confirmed that these are indeed LC50 values.

Dossier Submitter's Response

Comment 1: Agree, the BCF concept is not applicable to an inorganic compound.
Anyhow, what we mean is that the intact zeolite molecule is unlikely to pass membranes by diffusion.
We do describe and discuss in the report that constituents of the molecule, such as silver or zinc ions, may be taken up into the body.

Comment 2: The classification was based on studies made available by the applicant for silver zinc zeolite under the BPD, including a literature review. During peer review of the

CAR for silver zinc zeolite, the mentioned RIVM report became available. Since it appeared that Oncorhynchus mykiss was the chronically most sensitive species, with larval growth being the most sensitive endpoint (as in the previously evaluated Nebeker 1983 study), we evaluated the chronic studies with this fish species with the highest scrutiny. The studies were: (Dethloff et al. 2007), (Colin J. Brauner and Wood 2002b), (C. J. Brauner and Wood 2002a), (C. J. Brauner et al. 2003). Also these lately evaluated studies are involved with short-comings. The geometric mean is 0.08 µg/L, which is in the same interval as the previous NOEC of 0.02 µg/L. Thus, no change in classification nor M-factor is warranted. An excerpt from the recent updated version of the CAR is attached (Annex I), which contains comprehensive evaluation of the additional studies.

Comment 3: Indeed, we note the discrepancy. The evaluation of silver zinc zeolite under the BPR deals, however, only with the incorporation of the substance into polymers, which might serve as an explanation. We have no information how tightly the topically applied zeolites are attached to the material. Anyhow, this is not of importance for the classification and can be removed.

Comment 4: It should be LC50, of course. The numbers are correct.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	United Kingdom		MemberState	45

Comment received

We appreciate that the aquatic toxicity data included in the CLH Report principally relies on that included in the biocides review of silver zinc zeolite. However, we are unclear whether this review itself adequately considers all of the potentially relevant and reliable data available, particularly on silver. For the acute and chronic classification, a lot of reliance is placed on the study by Nebeker, et al., 1983 (on silver nitrate) yet several potential shortcomings are presented in relation to this study and how its results have been recalculated and interpreted in relation to hazard classification of silver zinc zeolite. We would appreciate confirmation that the key ecotoxicity endpoints from this and other studies have been finally agreed and used during the biocide peer review process. At 5.5.1.2 in relation to the Nebeker study, the 2012 RIVM report on 'Environmental risk limits for silver...' is remarked upon - and it also states that work is still ongoing to update the literature review which could affect M-factors. Other WFD EQS reviews of silver and zinc have been published but are not mentioned. A number of studies have also been completed on nanoforms of silver (and zinc), the aquatic toxicity of which appears largely driven by ionic metal and thus might well be relevant - but they are not included in the CLH report. We would therefore appreciate confirmation that all of the most relevant and reliable data and decisions relating to key aquatic toxicity endpoints for silver (and zinc) have indeed been used in relation to the proposed hazard classification. This is another reason why we feel that all available data on all forms of silver should ideally be considered together rather than in separate mixtures (see general comment).

We note that the 2012 RIVM EQS report on silver makes use of marine toxicity data and also geometric mean approaches in order to derive regulatory endpoints. The use of geomeans is also established for CLP where four or more values are available on the same/similar species (ref.: 4.1.3.2.4.3 in ECHA Guidance on the Application of the CLP Criteria). Could this approach be used here once all relevant acute and chronic endpoints

are considered?

The acute and chronic classifications are based principally on the toxicity of dissolved ionic silver in test waters - any dissipation due to adsorption to or transformation with particulates (inc. food), other organic matter (inc. dissolved), sulphates, sediments, etc. is discounted as a sufficient removal mechanism in more natural waters (although removal coefficients of 90-99.9% are reported and most monitoring reports v.low levels of untransformed ionic silver). Whilst this approach might be applicable for the acute classification and such removal mechanisms were tried unsuccessfully with copper classification, we feel that some further consideration of their potential relevance for the chronic classification of silver could be included and considered by the RAC - provided removal for silver can be shown to be sufficiently rapid, complete and irreversible in most natural waters.

Dossier Submitter's Response

Please note, this classification is made as a requirement for the approval of the biocidal active substance silver zinc zeolite. The whole approval process is on hold waiting for the RAC decision. Please, see our response to comment 44. The key ecotoxicity endpoints for aquatic toxicology have been finally agreed at the BPC-working group meeting in June 2015. We are aware that there were quite are a number of studies published dealing with toxicity of nano-sized silver particles after this report had been written, and many more are expected during the coming years. We do not have the possibility to scrutinise all these studies, which quite often provided very limited information (i.e. only one concentration tested) for risk assessment. Some studies even include soluble silver salts as reference for dissolved silver. So far we have not seen any that would change the present classification. Silver ions react quickly with sulfidic compounds and adsorb to particulate organic matter. However, this does not imply the substance is not available to animals. Particle feeders may take up the particle bound silver via food. Studies have shown that silver can be re-dissolved in the stomach, even sulfidic silver. We have discussed this in chapter 5.3 and the provided literature reviews.

RAC's response

Noted. Some further consideration on the environmental transformation is included in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2015	France		MemberState	46

Comment received

- FR agrees for the classification proposal
- It should be highlighted that the CLH report does not take into account the Ag nanoparticle issue (CLH report p 96)
- It seems that the Annex I with the literature review about bioaccumulation and magnification of silver is lacking.
- Section 5.5.1.2: 2: Other studies presented in the biocide dossier are not presented in this CLH report: Dethloff et al. 2007 – Colin J Brauner and Wood, 2002.

Dossier Submitter's Response

Please note, this classification is made as a requirement for the approval of the biocidal active substance silver zinc zeolite. This compound is not covered by the definition of nanomaterials (Commission Recommendation 2011/696/EU). This report does not attempt to classify silver, being it nano or other forms of silver.
Please, see our response to comment 44.

RAC's response
Noted.

NON-CONFIDENTIAL ATTACHMENTS RECEIVED

1. **Comments on the Proposal for Harmonised Classification and Labelling for Silver zinc zeolite** - submitted by Precious Metals and Rhenium Consortium (PMC) on 28/07/2015 [Please refer to comment no. 12, 27, 40, 43]
2. **Evaluation of Silver Substances under Regulation 528/2012** – submitted by Silver Task Force North America on 29/07/2015 [Please refer to comment no. 3, 15, 30]
3. **Comments on CLH Report: Proposal for Harmonised Classification and Labelling (Swedish Chemicals Agency regarding Silver Zinc Zeolite, April 13, 2015)** – submitted by Fuji Chemical Industries, Ltd. On 31/07/2015 [Please refer to comment no. 7, 18, 32]
4. **Comment Opinion on the Review of Silver Zinc Zeolite underthe European Biocidal Products Regulation** – submitted by Japanese Society of Industrial Technology for Antimicrobial Articles on 31/07/2015 [Please refer to comment no. 10, 21, 23, 35]
5. **Opinion on the Review of Silver Zinc Zeolite underthe European Biocidal Products Regulation** – submitted by Chinese Industry Association for Antimicrobial Materials on 31/07/2015 [Please refer to comment no. 11, 22, 24, 36]

CONFIDENTIAL ATTACHMENTS RECEIVED

1. **Comments on Carconigenticity of Silver Zinc Zeolite** – submitted by TNO on 30/07/2015 [Please refer to comment no. 1, 13, 28]
2. **Comments on Reproductive toxicology of Silver Zinc Zeolite** – submitted by TNO on 30/07/2015 [Please refer to comment no. 1, 13, 28]
3. **EU Silver Task Force expert opinion on the carcinogenicity and reproductive toxicity potential of silver and AEL derivation** – submitted by European BPR Silver Task Force on 29/07/2015 [Please refer to comment no. 2, 14, 29]
4. **Carcinogenicity of Silver Zinc Zeolite** - submitted by European BPR Silver Task Force on 29/07/2015 [Please refer to comment no. 2, 14]
5. **Reproductive Toxicology of Silver Zinc Zeolite** - submitted by European BPR Silver Task Force on 29/07/2015 [Please refer to comment no. 2, 29]
6. **Carcinogenic and Teratogenic Potential of Silver Zinc Zeolite** - submitted by European BPR Silver Task Force on 29/07/2015 [Please refer to comment no. 2, 14, 29]
7. **Evaluation of a two-generation study with silver zinc zeolite** - submitted by European BPR Silver Task Force on 29/07/2015 [Please refer to comment no. 2, 29]
8. **Reproductive and developmental toxicity of siver zinc zeolite.** August 10, 2012 COMMENTARY - submitted by European BPR Silver Task Force on 29/07/2015 [Please refer to comment no. 2, 29]
9. **Comments on the proposal for Harmonized Classification and Labelling of Silver Zinc Zeolite (Zeolite, LTA framework type, surface modified with silver and zinc ions) according to Regulation (EC) No 1272/2008 (CLP Regulation)** – Submitted by Sinanen Zeomic co. Ltd. On 31/07/2015 [Please refer to comment no. 8, 19, 26, 33, 38, 39]