Comments on

CLH Report: Proposal for Harmonised Classification and Labelling

(Swedish Chemicals Agency regarding Silver Zinc Zeolite, April 13, 2015)

Submitted to ECHA by

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Silver as an antimicrobial

Many metals demonstrate antimicrobial activity. This is related closely to their redox potential, which is in turn correlated with the solubility of the metal sulfides. Minimum inhibitory concentration (MIC) is a measure of the minimum concentration required to inhibit microbial proliferation – the lower the number, the more effective is the antimicrobial effect. Figure 1 shows the relationship between the MIC of various metal ions against the common bacterium E. coli and the solubility product K_{sp} of the corresponding sulfide – the product of the concentrations of the ions in aqueous solution. As shown, silver sulfide Ag_2S is virtually insoluble in water and the cation Ag^+ is highly effective in halting growth of E. coli. This is what is meant by "oligodynamic effect" – high efficacy at low concentration ("few" ions).

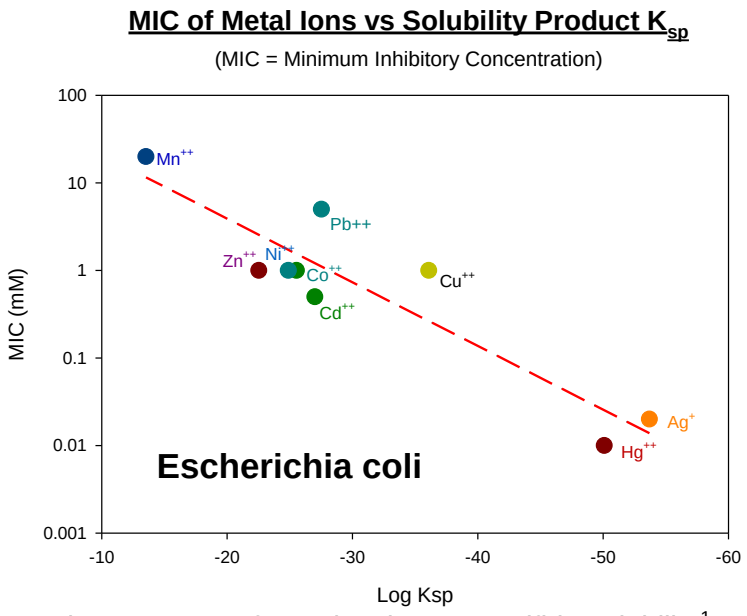

Figure 1. MIC of metal cations vs. sulfide solubility[1]

While there is no complete consensus about the mechanism(s) involved in silver's antimicrobial efficacy, a widely accepted and persuasive argument involves the binding of silver ions with thiols and disulfide groups in proteins and peptides associated with the microbial cell wall. This would explain why silver acts against bacteria but not mammalian (including human) cells, which have cell membranes rather than cell walls. It is also consistent with recent work suggesting that silver can help to prolong the useful lives of conventional antibiotics by distorting microbial cell walls and increasing their permeability -- allowing allow entry of not only antibiotics but also more silver ions, to bind with infracellular peptides and suppress microbial metabolism, respiration, and reproduction.[2] Restriction of such a valuable, long-standing aid to human health should not be lightly undertaken without convincing indications of actual risk.

[1]See D.H. Nies, "Microbial heavy-metal resistance," Appl Microbiol Biotechnol 51:730-750 (1999); A. Spain, "Implications of microbial heavy metal tolerance in the environment," Reviews in Undergraduate Research, Vol 2, 1-6 (2003). K_{sp} from literature, e.g. http://www4.ncsu.edu / ~franzen / public_html / CH201 / data / Solubility_Product_Const.

[2] J.R. Morones-Ramirez *et al.*, "Silver Enhances Antibiotic Activity against Gram-Negative Bacteria," Sci Transl Med 5, 190ra81 (2013)

Tight binding with sulfur-containing matter also reduces environmental effects of dissolved silver by locking it into essentially insoluble complexes and compounds.

Silver-zinc Zeolite

The author agrees with the statement of the Swedish Chemicals Agency ("Kemi") that "The active chemical entity in silver zinc zeolite is the silver ion released during use."[3] This is a silver antimicrobial. While zinc (and other metals) also show some antimicrobial activity, as shown in Figure 1, it is far lower than that of silver. The ion Ag^+ can readily exchanges with hydrogen ion H^+ (or H_3O^+), leaving an OH^- anion to react with a silver cation to produce AgOH and eventually Ag_2O – brown/black substances that discolor the material that the antimicrobial is intended to protect. Zinc is used to counter this effect by replacing monovalent Na^+ in the zeolite with bivalent Zn^{++}, which (because of the larger hydration sphere) has lower mobility, replaces two (more mobile) Na+ ions, and thus significantly reduces discoloration.

The author also agrees with the Kemi's explicit limitation of the report to "Zeolite, LTA framework type, surface-modified with silver and zinc ions," stating clearly that "This entry covers LTA framework type zeolite which has been surface-modified with both silver and zinc ions . . . ."[4] It should be noted in passing that most of the "surface-modification" is to internal surfaces within the highly porous LTA zeolite.

Zeolites are tecto-alumino-silicates; that is, they are very regular, 3-dimensional ("tecto"), highly porous crystals composed of tetrahedrons centered on aluminum and silicon atoms and linked through the oxygen atoms at the apices of the tetrahedra. As aluminum can form covalent bonds with only 3 oxygen atoms, each aluminum-centered tetrahedron requires an electro-sorbed cation for electrical neutrality. For steric reasons, two aluminum atoms cannot be linked by the same oxygen atom. These "rules" for zeolites are very simple – but generate well over a hundred distinct structures – including Linde Type A (LTA).[5]

Because the electrosorbed cations are fairly readily exchanged with other cations, zeolites are effective ion-exchange carriers; historically by far the major application of the LTA type, amounting to hundreds of millions of tons, has been as a "builder" in laundry detergents ("washing powder") to soften water by replacing calcium (responsible for "hard" water) with sodium – in place of environmentally damaging phosphates. Other uses include water softeners, dehumidification (adsorption on the high internal surface area) and catalysis.

Unfortunately, regulatory and classification organs world-wide still struggle to understand and classify zeolites, despite the devoted and enthusiastic efforts of the International Zeolite Association (IZA) to analyze, describe, and record in great detail the specific and definite structure of each type.[6] The USEPA still treats all zeolites as simple "mixtures" of oxides for purposes of the Toxic Substances Control Act ("TOSCA").[7] The Chemical Abstracts Service (CAS) of the American Chemical Society has at least a dozen registration numbers (CASRN) for various zeolites, all of which are listed as having "unspecified" structure – though IZA clearly describes and catalogues the structure of each.

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[3] CLH report, 2.1 (p. 11 and elsewhere).
[4] *Ibid.*, 1.1, p. 7
[5] See http://izasc-mirror.la.asu.edu/fmi/xsl/IZA-SC/ft.xsl
[6] *Ibid.*
[7] See http://www.epa.gov/oppt/newchems/pubs/mixtures.txt, "example 9"

The CASRN 130328-20-0 shown in the CLH report[8] for silver-zinc zeolite was issued on the basis of US Patents 4,911,898 and -899 and covers various types of zeolite (X, Y, Mordenite, etc.) in addition to the Linde Type A – which, in the sodium form used as the raw material for almost all commercial SZZ (and all the materials discussed in the Kemi CLH report), is CASRN 308060-12-0. The structure is shown in Figure 2.[9] This form was chosen because:

- The 1:1 molar ratio of Al to Si provides maximum capacity for exchangeable cations.
- The 4-Å openings between the β cavities allows for slow, controlled elution of Ag+ ions by diffusion through the structure.
- Stable manufacturing and high-volume use in laundry powders result in inexpensive and reliable supply.

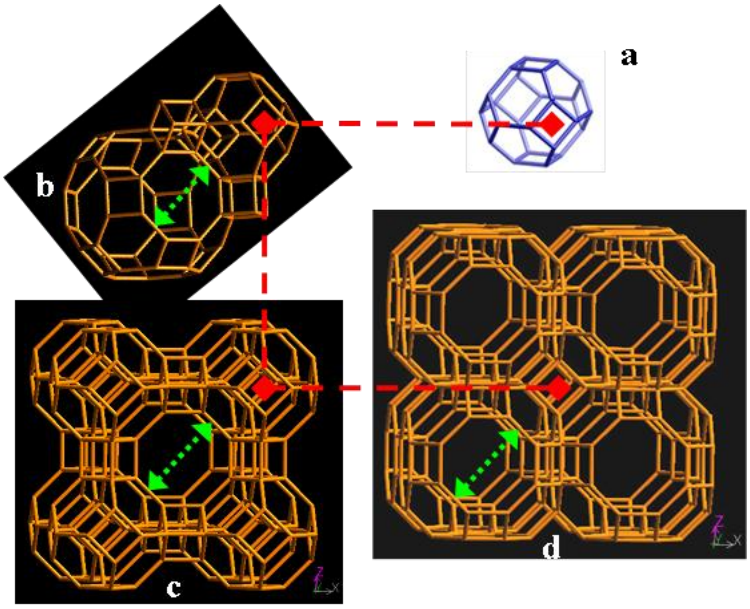

Figure 2: Structure of Zeolite A (LTA). Oxygen, adsorbed water, and exchangeable cations are omitted for clarity. (**a)** is the so-called "sod" sub-structure with 24 "T" atoms, 12 each of Al and Si; (**b**), (**c**), and (**d**) show increasingly larger structures. The dashed red lines connect the positions of one group of four atoms in each of the respective sketches. The pore opening (dotted green arrows) through the eight-sided oxygen-link ring is approximately 4.2 Å in diameter and opens into an 11.4 Å diameter "β cavity."

Solubility and ion-exchange

The difficulty encountered in properly understanding ion-exchange carriers is apparent in the discussion(s) of solubility. On page 13 of the Kemi CLH Report we read that "For the purpose of classification for environmental hazards, silver zinc zeolite is considered to be readily soluble. " On page 17, we are told that "silver zinc zeolite is not soluble in water and . . . the material only releases inorganic ions in water." On the same page it is "Not soluble with regards to the whole substance (substance as defined)." This statement is

[8] 1.1, P7, and elsewhere
[9] See the catalogue of the International Zeolite Association at http://izasc.ethz.ch/fmi/xsl/IZA-SC/ftc_fw.xsl?-db=Atlas_main&-lay=fw&-max=25&STC=LTA&-find

accompanied by some actual data – which unfortunately gives only partial insight to what happens in water.

The presumption is that this data is for particles of SZZ immersed alone in water – whereas in their actual application as materials preservatives, they would be embedded into polymer matrices. Given the restricted mobility of ionic silver within organic polymers, only particles at or protruding from polymer surfaces would be expected to elute ions; and with a particle of one µm in size, an ion starting at a site farthest away from the surface would have to make its way through some thousand 4 Å orifices and 1-nm β cavities, while surrounded by water molecules loosely bound to it in a hydration sphere. We can think of a charismatic (or controversial) politician making his way through the corridors and doorways of power while surrounded by a group of newspersons eagerly thrusting microphones.

There will be a difference in elution rate depending also on the content of the water in which the material is immersed. Due to colligative effects, ordinary salts dissolve more readily in pure water than in ionic solutions. With an ion-exchange carrier, on the other hand, a silver or other cation cannot emerge unless some other cation goes in to exchange with it; thus elution into (e.g. saline) is significantly faster than into pure water.

Another factor that must be taken into account is the size of the hydration sphere surrounding a dissolved ion, as a result of the polar nature of water molecules. Sphere size is correlated with the square of the ionic charge and the inverse of the effective ionic radius – that is, z^2/r. Therefore Zn^{++} has a significantly larger hydration sphere, and consequently lower ionic mobility, than Ag^+. In other data sets, though not in the data presented here in Table 9, it is apparent that elution of Zn^{++} can over time open the opportunity for Ag^+ to re-enter the zeolite, reducing silver concentration in the bath.

On page 25 we read of “potential effects of the carrier molecule” – but zeolite is an extensive and highly porous adsorptive crystal, not a “molecule.”

None of these details in itself leads to serious concern or complaint about Kemi’s findings, but these points do illustrate the misunderstandings and misinterpretations that can result from not fully understanding how ion-exchange carriers differ from soluble salts or other forms of silver.

Dose effects and risk

“Alle Ding' sind Gift, und nichts ohn' Gift; allein die Dosis macht, daß ein Ding kein Gift ist.“[10]

The author does take issue with Kemi’s findings on carcinogenicity and on reproductive toxicity, findings which could lead to in removal of SZZ from the European market despite more than three decades of active use without human health or environmental problems in Japan, the United States, and Europe. The findings are based upon a very limited group of studies involving continuous oral administration of massive doses of normally insoluble forms of silver to mice or rats. Extrapolation to human health is dubious, especially in the absence of sufficient attention to both dose and risk.

A discussion on toxicokinetics in 4.1.3 (p 31) mentions “Industry-sponsored published information [claiming] that zeolites may partially decompose during acidic conditions such as

[10] Paracelsus (1493-1541) – quoted on Wikipedia

in the stomach."[11] It is particularly unfortunate that suspicion of industry motivation and habitual reliance on (expensive, GLP) 3rd-party and academic investigations have resulted in overlooking what ought to be fairly fundamental matters of chemistry.

Carcinogenicity

The Kemi report states that, at the Technical Meeting stage, "there was no consensus whether or not to support a proposal for classification with respect to carcinogenicity in category 2."[12] The discussion of carcinogenicty[13] reports on studies of oral administration of SZZ to mice and rats over some period of time. Zeolite A, the LTA zeolite on which all this work is based, is stable down to a pH of about 4. In highly concentrated HCl (8M) it disintegrates completely and rapidly.[14] The pH of gastric acid in rat, mouse, and human stomachs is 1 to 3, and the Cl^- concentration is high (from the principle component of gastric acid, HCl). Under these circumstances the primary ionic form of silver will not be the cation Ag^+ (considered the main antimicrobial actor) but rather the anion dicholoroargantate $ClAgCl^-$ (or $AgCl_2^-$). Both forms will surely be present[15]; however the argentate (K_{sp} 7.5 x 10^{-6})[16] is much more soluble than the chloride AgCl (K_{sp} 1.8 x 10^{-10})[17] and will certainly predominate.

There appears to be little literature on dicholoroargentate. However it is more than reasonable to question whether studies involving this anion, resulting from (essentially neat, and continuous) administration of silver zeolite into rat/mouse stomachs, are relevant to a suspicion that the cation Ag+ might cause cancer in humans -- the classification recommended by Kemi.

Additionally, the dose relationships in this study are puzzling and suggest a need for further consideration before any final conclusion should be drawn. Though high-dose females showed some increase in tumors, high-dose mails showed fewer. Such confusions may be behind the lack of consensus at the Technical Meeting stage.

Reproductive Toxicity

The data central to the discusssion of reproductive toxicity in section 4.10[18] is also covered quite thoroughly in a series of publicly available USEPA Data Evaluation Reports.[19]

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[11] CLH Report, Section 4.1.3, p.31
[12] Section 2.1, p 11
[13] Section 4.9, p 66 ff
[14] Ryan L. Hartman and H. Scott Fogler, " Reaction Kinetics and Mechanisms of Zeolite Dissolution in Hydrochloric Acid," Ind. Eng. Chem. Res.2005,44,7738-7745 and "Understanding the Dissolution of Zeolites," Langmuir2007,23,5477-5484
[1515] Nicholas Tsipouras, Colin J. Rix, and Peter H. Brady, "Solubility of silver sulfadiazine in physiological media and relevance to treatment of thermal burns with silver sulfadiazine cream. Clin Chem 1995;41:87–91; and "Passage of silver ions through membrane-mimetic materials, and its relevance to treatment of burn wounds with silver sulfadiazine cream," Clinical Chemistry 43:2 290 – 301 (1997)
[16] Martin Allen, "The dissociation constant of dichloro-argentate ion," abstract *in Proceedings of the Indiana Academy of Science*, Volume 62, 1952, p. 144, based on data from Jonte, J. H., and D. S. Martin, Jr. 1952. "The solubility of silver chloride and the formation of complexes in chloride solution," J. Amer. Chem. Soc. 74 :2052-2054
[17] Or 1.77 x 10^{-10} – value widely available in the literature
[18] Kemi CLH Report, p.73 ff

In these DER's the materials discussed are silver zinc zeolites, although incorrectly classified in the DER's as having silver nitrate as the active ingredient. (Silver nitrate is the soluble form of silver used for the exchange of Ag^+ cations into the LTA zeolite carrier.) In these cases neither the manufacturer nor USEPA regard the significant content of zinc (as much as about 20%) as an "active ingredient." The the reason for inclusion of zinc is to reduce discoloration rather than for antimicrobial efficacy.

As in the carcinogenicity study discussed above, high doses of SZZ were fed over protracted periods directly into rat stomachs. Again, the principle silver species will surely have been the anion dichloroargentate – not the Ag^+ cation. Mortality was encountered in all generations. Dose response correlation is unclear. As is clear from the DER's the data was carefully reviewed by USEPA; the outcome did not impede acceptance of the study and registration of the products by USEPA..

The Kemi report also refers to a well-known 2005 study by Shavlovski et al.,[20] in which high doses of silver chloride AgCl were administered continuously to rats, leading eventually to the birth of pups who were unable to survive. The authors attributed this to suppression of copper metabolism, specifically to reductions in ceruloplasmin and superoxide dismutase, rendering the pups unable to survive in air. This conclusion is strongly supported by the later work of Ilyachova,[21] with Shavlovsy as a co-author, demonstrating that simple intraperitoneal injection of copper sulfate was an effective antidote. Once again, the soluble species of silver in the highly acidic, high-chlorine murine stomach was surely dichloroargentate and not Ag^+. Extrapolation of these highly specific results to suggest potential damage to unborn human children as a result of the antimicrobial use of Ag^+-eluting SZZ used to preserve organic materials (uses detailed in the report[22]) is hardly appropriate or convincing.

Mention is also made of a published study with silver acetate[23] that failed to show a clear dose-response relationship. The author and the US silver task force are aware of yet another (screening) study in rats, completed by a US governmental body on July 31, 2012 but still unpublished and quite possibly not publishable. The study was designed to investigate examine thymic atrophy – which was not found. Here again there was no clear dose-response finding. Silver acetate was chosen for its high water solubility and inoffensive anion. Kemi makes an "assumption that silver acetate is completely dissolved in the stomach";[24] but with this species also, the high chlorine content and the low solubility of AgCl compared to dichloroargentate makes it virtually inevitable that that the primary dissolved silver species in these studies with silver acetate was also the anionic dicholoroargentate – not Ag^+.

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[19] Available at http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/cleared-reviews/reviews/072503/072503.htm

[20] Mikhail M. Shavlovski et al., "Embryotoxicity of silver ions is diminished by ceruloplasmin -- further evidence for its role in the transport of copper," BioMetals 1995, 8,122-128

[21] Ekaterina Ilyechova et el., (including Michael Shavlovsky) "Experimental switching of copper status in laboratory rodents" Journal of Trace Elements in Medicine and Biology 25 (2011) 27–35

[22] Listing in Kemi report, pp 20-21 – includes primarily incorporation into organic matrices to protect the materials themselves

[23] Kemi CLH Report, pp. 85-86

[24] Kemi CLH Report, p. 85

Closing remarks

While respecting the diligent and comprehensive investigation by the Swedish Chemicals Agency, the author believes it is based on incomplete understanding of ion-exchange materials and mechanisms and – as is all too often experienced this field – incomplete understanding of or attention to the antimicrobial mechanism of silver, too ready extrapolation between species both of mammals (murine and human) and of silver (cations and anions). Silver zinc zeolite, like other sources of the silver cation, is an important aid for advancement of human health with full respect for the natural environment; the case for banishment at this time is, at best, “not proven.“

It is perhaps inevevitable, but most unfortunate, that the regulatory requirement for limitation of hazards (too often with inadequate consideration of actual risk) frequently requires significant expenditure of resources in the attempt to demonstrate “negatives,“ and thus diverts resources from forward-looking efforts to elucidate mechanisms and develop materials and products to support both health and the environment. The author (and Fuji Chemical Industries) fully intend to continue their efforts of the last several decades on behalf of silver antimicrobials.

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Author's details and qualifications

Academic: BA, *cum laude*, Chemistry and Physics (joint degree), Harvard College, 1961; MA, Area Studies, Far East (Harvard GSAS. 1962); six further years study toward PhD in Far Eastern Languages (Chinese, Japanese, Altaic; Harvard GSAS; "all but dissertation."); Oveseas Fellow, Kyoto University, 1988-1970 (Manchu)

Employment: Design and manufacture of UV spectrographic analytic equipment, Baird-Atomic Inc., 1960-1967; Teaching Fellow, Harvard GSAS 1962-1965; Lecturer, Doshisha University, Kyoto (1968-1965); Kanebo, Ltd., 1968 – 1999 (Assistant to President and Manager, International Department, Osaka, to 1974; Assistant Chief US Representative, New York, 1974-1998 -- includes the period of USEPA registration of Kanebo's silver zeolites as the first antimicrobial uses of silver beyond swimming pools and charcoal filters, and the first silver materials preservatives); President of several Kanebo US subsidiaries including Kanebo Information Systems; Kanebo USA; and Kanebo Zeolite USA, 1994 – 1999; President and owner, American Technical Trading (1999 – present); consultant and Advisor (International) to Fuji Chemical Industries, purchasor of the silver antimicrobials business of Kanebo, Ltd.

Industry: Administrative Committee, Silver Task Force North America, 2013 - present; Administrative Committee and Co-chair, Zinc Task Force North America, 2014-present

Languages: English and Japanese, others less fluent.