



European Precious Metals Federation

# Carcinogenicity testing silver - heads-up conf call

19 December 2019

# Introduction

## Silver Containing Active Substances (SCAS)

- **Registered under BPR by ESTF:**
  - *Silver (metallic)*
  - *Silver (reaction mass with SiO<sub>2</sub>; nano)*
  - *Silver nitrate*
  - *Silver chloride*
  - *Silver chloride (reaction mass with TiO<sub>2</sub>)*
  - *Silver phosphate glass*
  - *Silver zinc zeolite (SZZ)*
  - *Silver copper zeolite (SCZ)*
  - *Silver zeolite (SZ)*
  - *Silver sodium hydrogen zirconium phosphate (SSHZP)*
- **Data requirements incl. human health endpoints**
- **Obligation evaluating member state to submit CLH-proposal**
- **SCAS evaluating MS: Sweden (KEMI)**



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**Focus of today's call: carcinogenicity endpoint**



# SCAS carcinogenicity

## Carc endpoint coverage by ESTF:

- **Experimental studies (OECD453)**
  - SZZ (Silver Zinc Zeolite) as test item
  - Test on mice and rat  
(Takizawa, 1992)



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## *EPMF Ag dossiers*

- *no carcinogenicity test data*
- *waiving statement based on absence of*
  - 1. mutagenic potential (via weight-of-evidence) and*
  - 2. reliable human data indicating any concern for carcinogenicity (despite long history of use)*

# SCAS carcinogenicity

## Carc endpoint coverage by ESTF:

- Experimental studies (OECD453)
- **KEMI CLH report SZZ (2015)**

*“Results of a chronic toxicity/carcinogenicity study in rat indicate that silver zinc zeolite AgION Antimicrobial Type AJ causes statistically significant positive trends for leukaemia in both sexes and pituitary adenomas in females. The tumour types could not be dismissed as it is considered unlikely that positive trends, in which all doses are considered, appear by chance and there was no reason to disregard results in the concurrent controls. If the substance has an ability to promote initiated cells into tumours, an increased frequency of those tumour types common to the strain used seems reasonable.”*

→ **classify as Carc 2** (H351; suspected of causing cancer)



# SCAS carcinogenicity

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- **Public consultation + RAC opinion (Dec 2015)**

*“...no epidemiological evidence ... in humans, a classification in Category 1A is not appropriate. RAC also considers that the animal evidence is insufficient for classification in category 1B. RAC considers that a classification in category 2 is not appropriate based on the weight of evidence analysis above and the comparison of the findings with the CLP criteria. ... Thus, RAC considers that, based on the weight of the evidence analysis of carcinogenicity, **SZZ does not warrant classification for carcinogenicity.**”*



# SCAS carcinogenicity

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- **CLP ATP 10 (May 2017): NO classification for carcinogenicity**

(iii) the following entries are inserted in accordance with the order of the entries set out in Table 3:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling	
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)
047-003-00-3	silver zinc zeolite (Zeolite, LTA framework type, surface-modified with silver and zinc ions)  [This entry covers LTA (Linde Type A) framework type zeolite which has been surface-modified with both silver and zinc ions at contents Ag+ 0,5 %-6 %, Zn2 + 5 %-16 %, and potentially with phosphorus, NH4+, Mg2+ and/or Ca2+ each at level < 3 %]	—	130328-20-0	Repr. 2 Skin Irrit. 2 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	H361d H315 H318 H400 H410	GHS08 GHS05 GHS09 Dgr	H361d H315 H318 H410



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**Read-across** from SZZ study to

- **other zeolite dossiers (SZ, SCZ) and**
- **Ag containing materials** (like SSHCZP, silver chloride (reaction mass with TiO<sub>2</sub>), Silver phosphate glass)

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**QUESTION:** justified read-across to

1. **Ag containing materials (cfr. above)?**
2. **other Ag forms (Ag nitrate, metallic Ag...)**

# SCAS carcinogenicity testing

**KEMI:** - strong focus on Reprotox cat1 (BPR exclusion criterion!)  
- no focus on carcinogenicity endpoint

**COMM:** all CMR endpoints to be considered in parallel



**Urgency to consider carcinogenicity**



# SCAS carcinogenicity testing

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**Urgency to consider carcinogenicity**

**KEMI:** carcinogenicity endpoint not reliably covered

→ carcinogenicity study needed

→ **approved by Biocides WG**



# SCAS carcinogenicity testing

## Meeting KEMI – ESTF (9 Dec 2019)

- ESTF proposal to perform in vivo toxicokinetics on SCAS  
→ aim: read-across from existing carcinogenicity study
- KEMI agreed to re-consider need for testing  
→ ESTF to submit (written) justification <mid Jan 2020

### *Next steps:*

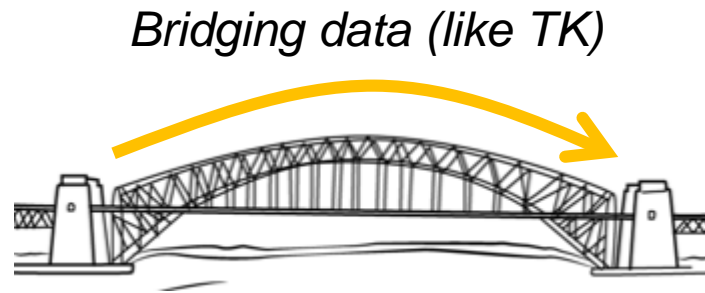
- *KEMI to re-consider position*
- *KEMI to re-consider/decide with other MS*
- ***Decision expected end Feb 2020***  
→ ***UNLIKELY that carcinogenicity testing won't be requested***



# SCAS carcinogenicity testing

## Read-across under REACH

Experimental study with  
'worst-case' test item



Read-across  
experimental data to  
other substances



# SCAS carcinogenicity testing

Read-across under REACH:

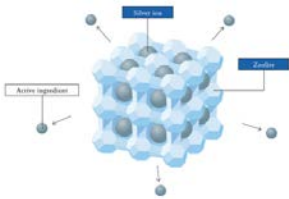
Experimental study with  
'worst-case' test item

*Bridging data (like TK)*



Read-across  
experimental data to  
other substances

SZZ as worst case?

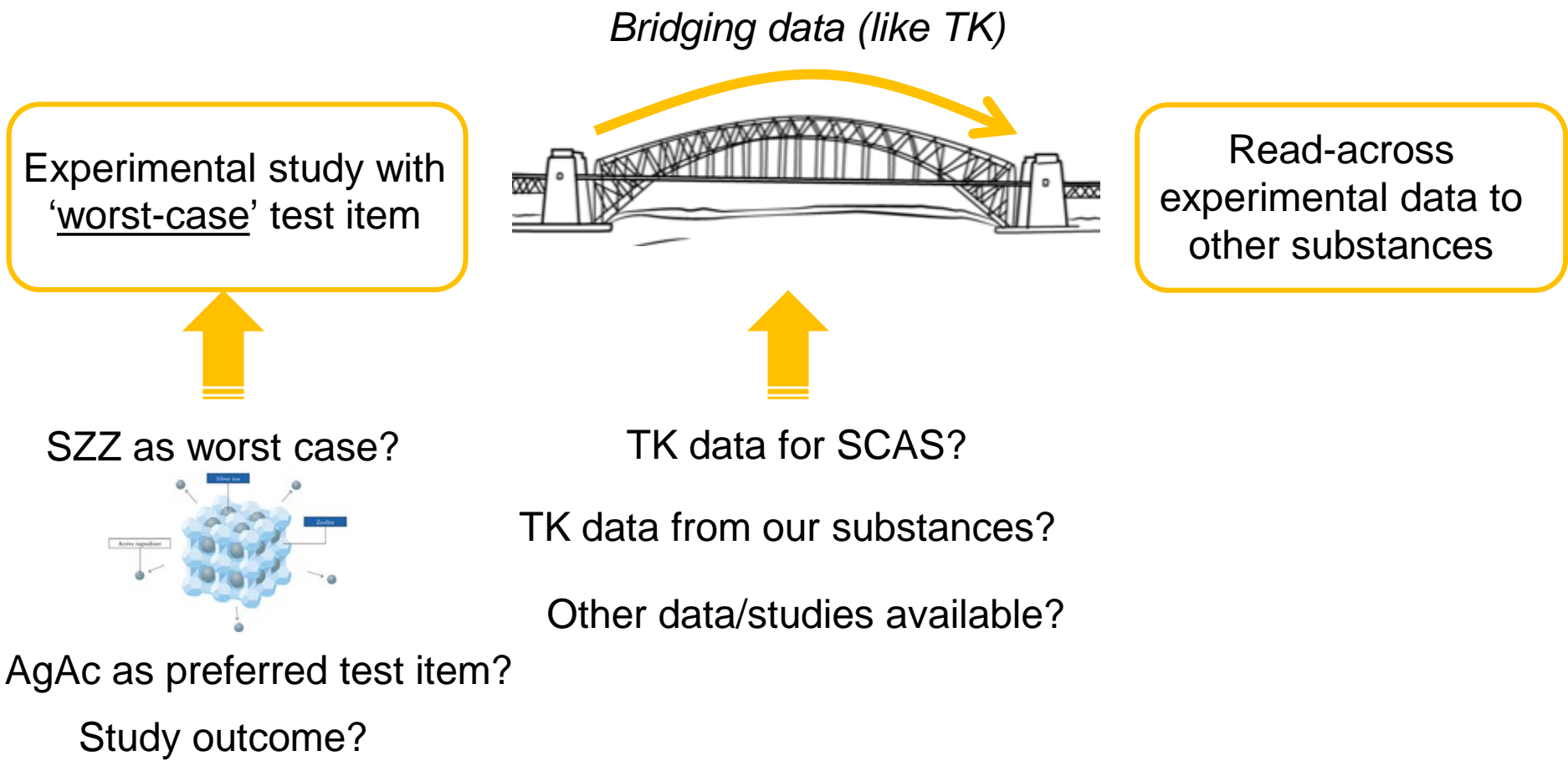


AgAc as preferred test item?

Study outcome?

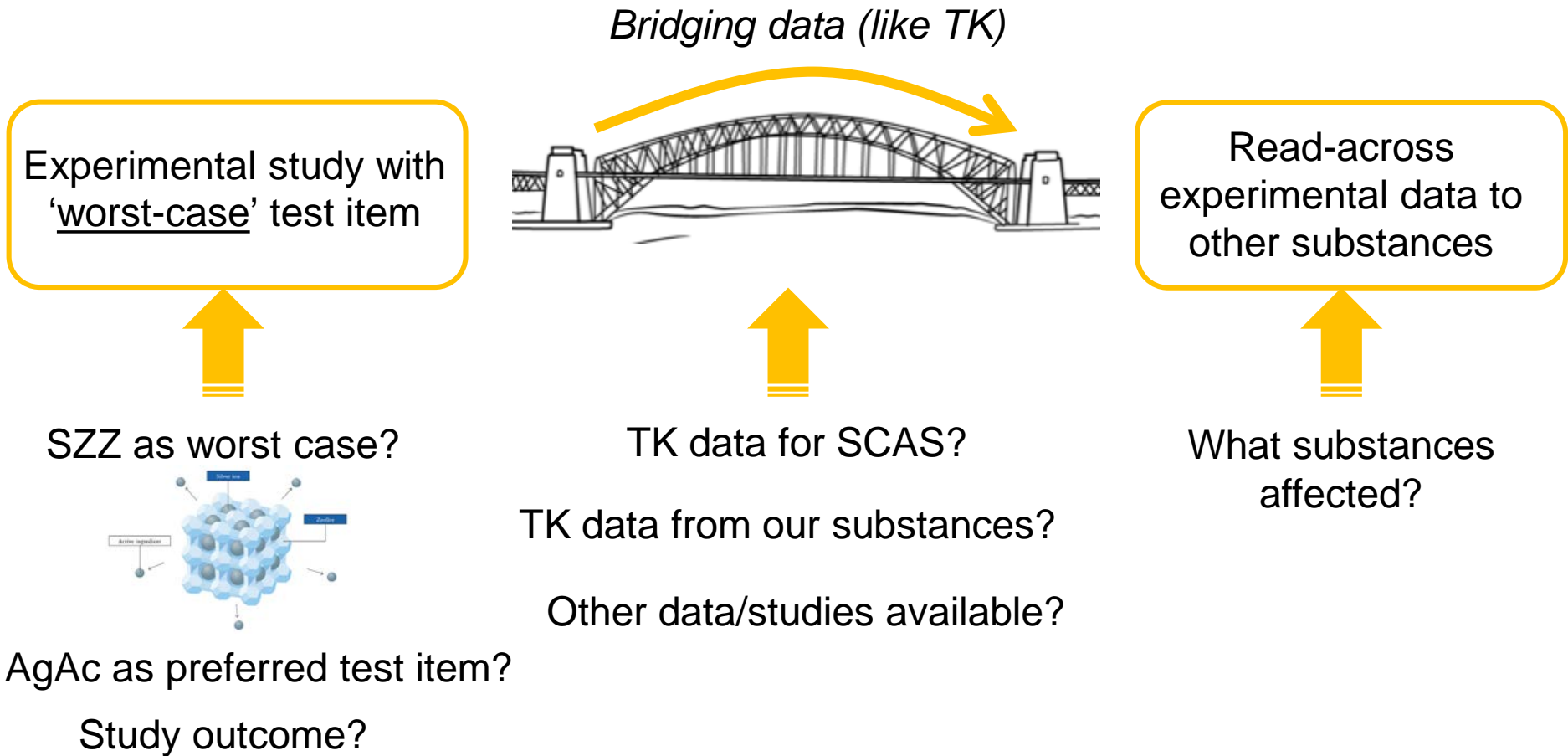
# SCAS carcinogenicity testing

## Read-across under REACH:



# SCAS carcinogenicity testing

## Read-across under REACH:



## EPMF secretariat...

1. ... considers **SZZ not as worst-case** test item
2. ... not aware of existence **reliable TK data for SCAS**  
→ read-across from SZZ to all SCAS unlikely
3. ... considers **request new carcinogenicity test** very likely
4. ... considers request for '**soluble Ag cmpd**' as **test item** very likely  
→ read-across to our REACH dossiers very likely  
→ need to access to study + include in dossiers
5. ... proposes to closely monitor developments (via ESTF)
6. ... proposes involvement in carcinogenicity test
  - **cost-sharing** (+€2M in total)
  - **study design / monitoring & data interpretation**

**(co-)lead the carcinogenicity test  
to ensure highly reliable endpoint coverage**





# THANK YOU

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