Comment on the planned dossier proposing harmonized classification and labelling for 1,2-benzisothiazol-3(2H)-one [BIT], CAS RN 2634-33-5, EC 220-120-9, concerning the Specific Concentration Limit (SCL) for skin sensitization

Wacker Chemie AG, May 2021

1. Summary

- *WACKER supports the suggestion by the Spanish dossier submitter to keep the current specific concentration limit (SCL) for skin sensitization at 500 ppm for 1,2-benzisothiazol-3(2H)-one (BIT). This value is supported by the toxicological data and reflects the hazard potential of BIT.*
- *The 500-ppm value is also justified in comparison with the defined SCL of other isothiazolinones, as it takes into consideration the difference in their relative sensitization potential and the substance-specificity.*

2. Introduction

Wacker Chemie AG is a specialty chemicals company, with a leading market portfolio of water-based binders based on vinyl acetate-ethylene (VAE) polymers for over 150 customers globally for the construction sector, adhesives, paints, coatings, paper and board manufacture and many others.[1] The use of active substances for in-can preservation is an inevitable part of the formulation process. In the following contribution we would like to voice our support for the proposed SCL for skin sensitizer (500 ppm) submitted by the Spanish dossier, as this classification corresponds to our internal assessments of ensuring the continued safe use of BIT as an effective in-can preservative.

3. Efficacy and application of BIT for in-can preservation (PT6)

1,2-benzisothiazol-3(2H)-one, CAS RN 2634-33-5 (BIT) is a broadly used preservative for water-based formulations. As a producer of water-based dispersions, having an efficient preservation is highly important for our products. Since microorganisms find ideal growth conditions, microbial deterioration needs to be avoided to ensure that our products can safely be used, sustain their functionality, and have the necessary shelf-life.

BIT is one of the few remaining effective in-can preservatives, which we have safely used in our products for decades.

[1] Wacker Polymers : https://www.wacker.com/cms/en-us/products/product-groups/polymer-dispersions/polymer-dispersions.html (2021).

Due to regulatory restrictions, fewer and fewer preservatives remain available, which makes efficient preservation increasingly difficult and threatens the future of water-based formulations. One reason is the impact of the harmonized classification on the approval process of the active substance under the Biocidal Products Regulations. In the case of the isothiazolinones the SCL for skin sensitization is especially important and hence we would like to comment on this hazard class specifically.

4. SCL for skin sensitization: 500 ppm is supported by toxicological data

Table 1: Comparison of skin sensitizing properties of several thiazolinones (RAC Opinion OIT 2018)

Substance	**MBIT**	**BIT**	**MIT**	**CMIT/MIT (3:1)**	**OIT**
CAS RN	**(CAS 2527-66-4)**	**(CAS 2634-33--5)**	**(CAS 2682-20-4)**	**(CAS 55965-84-9)**	**(CAS 26530-20-1)**
LLNA	EC3 = 1.04 % EC3 = 0.69 %	EC3 = 2.3 % EC3 = 32.4 % EC3 = 4.8 % EC3 = 10.4 %	EC3 = 0.86 %	EC3 = 0.003 % EC3 = 0.007 %	EC3 = 0.46 % EC3 = 0.66 % EC3 = 0.24 %
Classification	Skin Sens. 1A	Skin Sens. 1	Skin Sens. 1A	Skin Sens. 1A	Skin Sens. 1A
HRIPT	9/45 (20 %) volunteers showed dermal sensitization at 500 ppm	5/58 (9 %) at 725 ppm aq., 0/54 (0 %) at 360 ppm aq.	1/116 (0.9 %) volunteers at 400 ppm and 1/210 (0.5 %) at 500 ppm	-	0/103 subjects at 50 ppm (0.005 %) 1/222 (0.45 %) subjects at 100 ppm (0.01 %)
Current SCL	0.0015 %	0.05 %	0.0015 %	0.0015 %	0.0015 %

Comprehensive data are available for BIT regarding testing for skin sensitization. The data include results from the OECD test TG 429 as well as TG 406 (CLH report Spain, 2021). Furthermore, human data are available from individual observations and from systematic human patch tests (HRIPT) by dermatological investigations on larger numbers of patients (e.g. Alomar A. et al., 1984, or Andersen K.E. and Veien N.K., 1984 and 1985). Based on the available data, BIT is undoubtedly a sensitizer, as are all members of the isothiazolinone family. Therefore, classification as **Skin Sens. 1; H317** (may cause allergic skin reactions) is warranted.

Specific Concentration Limit

Table 1 gives an overview of the key results of different isothiazolinones including BIT (RAC Opinion OIT, 2018).

Obviously, the obtained EC_3 values of BIT differ significantly from the others of the isothiazolinone family. The results of the LLNA studies indicate that BIT, in contrast to the other isothiazolinones, is rather a moderate sensitizer (corresponding to category 1B at EC_3 values > 2 %). The results from GPMTs also give a comparable picture (BIT sensitize more than 30% of animals after challenges with intradermal doses higher than 1%).

In this context it is important to understand the sensitization process as a highly specific two-stage immune reaction, which is started by the formation of an antigen(BIT)-protein-complex. Apparently, considering the available data, a higher induction threshold can be assumed in the case of BIT than for other isothiazolinones. This presence of a higher induction threshold is well supported by the obtained EC_3 values in the LLNA studies and by the available human data (Alomar A. et al., 1984, or Andersen K.E. and Veien N.K., 1984 and 1985).

In the majority of cases of human patch tests, sensitization is observed at (predominantly) 1000 ppm, but not at < 500 ppm or only with very low incidences or unclear boundary conditions. It could be that the affected persons are already sensitized by BIT and the 10-fold lower threshold for elicitation was triggered. Considering all available data, it can be assumed that a SCL of 500 ppm adequately reflects the hazard potential of BIT. Already sensitized persons are protected by the hazard statement EUH208 (Contains <BIT>. May produce an allergic reaction) with a derived limit of 50 ppm.

Wacker Chemie AG therefore supports the argumentation of the Spanish dossier submitter to retain the current SCL of 500 ppm.

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