Verband der deutschen Lack- und Druckfarbenindustrie e.V.

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Comment on the planned harmonized classification and labelling of BIT concerning the Specific Concentration Limit for skin sensitization

Executive Summary

Benzisothiazolinone (BIT) is a highly important preservative for water-based formulations, for instance for paints, coatings and inks. As fewer and fewer preservatives remain available for this purpose, the future of water-based formulations is under threat. The harmonized classification under CLP has a significant impact on the approval process of the active substance under the Biocidal Products Regulations. In the case of the isothiazolinones the specific concentration limit (SCL) for skin sensitization is especially important, as the SCL has been applied as a limit value for the use in products for the general public in the risk assessment during the approval process of the BPR. If the SCL is below the concentration needed for efficacy the result is expected to be a de facto ban for consumer products.

The current harmonized classification of BIT shall be updated. Within the CLH process the dossier submitter suggests keeping the current SCL for skin sensitization at 500 ppm for BIT. VdL agrees with this proposal, which is well supported by the available toxicological data. Furthermore, this is also justified in comparison with the defined SCLs of the other isothiazolinones and their relative sensitization potentials. Experience has shown that in the case of the isothiazolinones the ECHA Risk Assessment Committee tends to overlook the different sensitization potential of the individual isothiazolinones and decide to apply the same SCL for all isothiazolinones , despite different SCL proposals from the dossier submitter. However, setting the same SCL of 15 ppm for BIT as for the other isothiazolinones is neither toxicologically justified, nor does it improve consumer protection simply because it would be banned. Hence, VdL supports the proposal detailed out in the CLH dossier prepared by the Spanish authority.

Introduction

On September 16th 2020 the Spanish authorities submitted a dossier for a revised harmonized classification according to regulation (EC) No. 1272/2008 for 1,2-benzisothiazol-3(2H)-one (**BIT**, CAS No. 2634-33-5). The following classification is proposed:

Acute Tox. 4, H302
Acute Tox. 2, H330
Eye Dam. 1, H318
Skin Sens. 1B, H317, SCL=0,05 %
Aquatic Acute 1, H400
Aquatic Acute 1, M-factor=1
Aquatic Chronic 1, H410
Aquatic Chronic 1, M-factor=1
Oral: ATE = 454 mg/kg

Inhalation: ATE = 0.25 mg/L

Due to the high importance of this substance as an active for in-can preservation in the paints, coatings and ink industry, but also for many other sectors, we would like to comment on the proposed classification as skin sensitizer. The corresponding specific concentration limit (SCL) may have a high impact on the future use of BIT as a preservative.

VdL agrees with the classification proposal and suggest classifying BIT accordingly. However, experience has shown that in the case of the isothiazolinones the ECHA Risk Assessment Committee tends to overlook the different sensitization potential of the individual isothiazolinones and decide to apply the same SCL for all isothiazolinones, despite different SCL proposals from the dossier submitter.

In this document we would like to support the dossier submitter's proposal of keeping the current SCL of 500 ppm since it is well supported by the available toxicological data, and it seems highly justified when comparing it with the relative sensitization potential of the other isothiazolinones. It is a more than reasonable approach in terms of consumer protection.

Importance of BIT for the preservation of paints and coatings

BIT is used as a preservative for products during storage (in-can preservative, PT 6) in the framework of the biocidal products regulation (BPR)[1]. As microorganisms find ideal growth conditions in water-based paints and coatings, preservatives are indispensable for most solvent-free, water-based paints, coatings and printing inks: they prolong their shelf life and prevent mould formation and bacterial growth. One of the most important properties of a biocide is their broad-spectrum efficacy. Thus, it is not enough if it affects a specific harmful organism in a targeted way as it depends on many factors (production conditions, raw material contamination, etc.) which bacteria are present, and this is generally unknown in advance. Furthermore, the active substance must be compatible with the respective matrix. In this way, the oxygen sensitivity and the stability in the right pH value range play a critical role as well as the odour or potential discolourations. Hence, only few of the in-can preservatives listed in the ECHA BPR article 95 list can be used for paints, coatings and inks. Due to the large number of harmful organisms and potential resistances, it is thus necessary to maintain a range of active substances and the possibility of combining them. Especially in the do-it-yourself sector, it is emerging that this might no longer be safeguarded in the future, due to regulatory restrictions. This threatens the future of water-based paints and coatings. It needs to be stressed that over 70% of the production volume of paints and coatings in Germany is water-based. Looking at the German market for paints and coatings, we estimate that roughly half of the market with a real value of Euro 2.6 billion is affected.

BIT is one of the last remaining rather broadly applicable actives for the preservation of paints, coatings and inks. It shows efficacy against bacteria, fungi and yeasts and is very stable, even at high pH values and is easy to combine. Furthermore, it has a very low volatility[2], which is

[1] Regulation (EU) No 528/2012

[2] Vapour pressure in Pa 0,000006 (20 °C), Helge Kramberger, Konservierung wasserbasierter Produkte: Isothiazolinone in Innenräumen, Gebäudeschadstoffe und Innenraumluft, Band 6, 2018

important for indoor applications. BIT is typically used in combination with other actives (to cover gaps in the efficacy) at a dosage of 100 to 500 ppm.

Potential Impact of the SCL for skin sensitization for the use as preservative

The restrictions within the framework of the approval process under the BPR are the main problems for in-can preservatives. In the case of isothiazolinones, the specific concentration limits for skin sensitization are being constantly lowered in the CLH process. As this limit value has resulted in a restriction on the sale for treated articles for the general public[3] in the approval process, this is expected to lead to a crisis for the paint industry as the consumer market will diminish. Many active substances, such as for example MIT, are not efficacious below the proposed limit value. If, at the end of this process, this limit value should be in force for all isothiazolinones, then according to the estimation of our experts, no adequate preservation can be ensured in the future.

The reason for the restriction for consumer uses in concentrations above the SCL– as we understand it – is the assumption that private consumers are not capable of avoiding reversible effects on the skin (e .g. redness, rashes) even though the label on the packaging warns about such effects (hazard phrase and pictogram). This assumption has been used for one active substance approval already (C(M)IT/MIT, Regulation (EU) 2016/131)[4]) and it may be expected to be applied for the other actives as well. In the case of C(M)IT/MIT the SCL may be justified and this biocide is still effective at concentrations below its SCL. However, this is not the case for the other members of the isothiazolinone family.

The need to consider substance-specificity in setting the SCLs for induction of skin sensitization

It is important to stress that we are not opposing the setting of SCLs for the isothiazolinones. However, we strongly believe that the substance-specificity needs to be considered. According to CLP regulation the **hazard classification** (H317) is based on **induction of skin sensitization** while **the information phrase** that a mixture contains an allergen (EUH208) is based on **elicitation of an allergic response**. The EUH208 (triggered by 1/10 of the SCL for skin sensitization) is meant to inform those individuals already sensitized to the substance.

It is certain that human data from dermatological clinics **indicate elicitation** of an allergic response (EUH208) rather than induction of sensitization (H317). The cause and extent of past exposures of the patients cannot be quantified as it is impossible to get this information from the relevant medical history (anamnesis), i. e. retrospectively. As reported in the RAC opinions on the other isothiazolinones the human case studies cannot be validated, lack details and do not show dose-response but need to “be considered as supporting additional evidence”. Using case studies to derive intrinsic hazard properties is problematic. This is especially true if the exposure varies for different applications. It is a fact that the longer the duration and the more frequent the exposure to an allergen, the more cases of allergy would be expected. While the exposure to products like e. g. paints is infrequent and non-

[3] CA-Sept13-Doc.6.2.a.rev1, Authorisation of skin sensitizer biocidal products requiring PPE for non-professional users

[4] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0131&from=EN

intentional other uses might cause frequent and intentional exposures. Therefore, potency (as defined by the SCL) **is a relative term** and should only be used to rank/differentiate the various sensitizers accordingly. Thus, when defining SCLs for hazard classification, use of such case studies for setting SCLs for **induction** of skin sensitization (i.e. hazard classification) is not appropriate. The conclusions should rather be based on results of validated studies where the **exposure is standardized** i.e. animal studies or even well-controlled Human Repeated Insult Patch Tests (HRIPTs). The local lymph node assay (LLNA, OECD 429) represents such a well-validated study.

Local lymph node assays (LLNAs) show that the potencies of skin sensitization **induction** are quite different for the various isothiazolinones. The results[5] from the LLNAs (taking the average of the EC3 values) demonstrate that the potencies relative to C(M)IT/MIT (3:1) are as follows:

Substance	**C(M)IT/MIT**	**DCOIT**	**OIT**	**MIT**	**MBIT**	**BIT**
Relative potency	1	1/6	1/90	1/170	1/170	1/2500
SCL (ppm)	15	15	15	15	15	500
EC_3 value	0.003 % 0.007 %	0.03 %	0.46 % 0.66 % 0.24 %	0.86 %	1.04 % 0.69 %	2.3 % 32.4 % 4.8 % 10.4 %

This means that e. g. OIT would be significantly less potent than C(M)IT/MIT in inducing skin sensitization and following this logic OIT should have a significantly higher SCL. However, RAC has assigned the same SCL (i. e. 15 ppm) for all the above listed isothiazolones listed above, with the exception of BIT. The proposals of the member states reflected the differences in potency and hence the substance-specificity, however, this was levelled by the decisions taken by RAC. Hence, the difference in potency of different representatives of the isothiazolinones is not reflected, which leads to a detrimental levelling, which is also not in line with consumer protection goals (see below).

Available data for the skin sensitizing potency of BIT

Concerning the sensitization potency of BIT several validated studies, where the exposure is standardized, are available.[6] These studies have also been summarized in previous RAC opinions on other isothiazolinones.

[5] Page 13 in the RAC opinion for MBIT (https://echa.europa.eu/documents/10162/708c2c4e-7b66-51f5-14c2-1090e8203227), page 15 in the RAC opinion for OIT (https://echa.europa.eu/documents/10162/4f2ebbc7-d814-f967-12bb-223c17b9aeec), p 17 RAC opinion for DCOIT (https://echa.europa.eu/documents/10162/c5397851-ef29-13b1-24ae-a213c967ad38)

[6] Gerberick et al., 2005 in Contact Dermatitis 16(4):157-202
Botham et al., 1991 in Contact Dermatitis 25(3):172-177
Basketter et al., 1999 in Contact dermatitis 40(3):150-154
Quintiles England limited, Project Code A/K/42557 "Skin Sensitization Study In The Guinea Pig Magnusson and Kligman Maximisation Test" (Sponsor: H&C Prom Kemi ApS, joint ownership: Prom Chem Ltd and Thor GmbH), 02-1997
psl - product safety labs, Study No. 3863 "Dermal sensitization test – Buehler Method" (Sponsor: Hüls America Inc., joint ownership: Prom Chem Ltd and Thor GmbH), 24-01-1996

Non-human data

Mouse Local Lymph Node Assay (LLNA, OECD 429)

There are different **LLNA tests** from 1991, 1999 and 2005, giving EC3 values of 4.8%, 32.4%, 10.4%, 2.3%, respectively.

According to table 3.6. of the Guidance on the Application of the CLP criteria[7] this clearly indicates a **moderate sensitizer** (EC3 > 2, **Skin Sens 1 B**).

Guinea Pig Maximisation Test (OECD 406)

Following challenge, 9 out of 20 animals in the test group reacted positively to 10% w/v test article in ethanol at 24 or 48-hour examinations, giving a response incidence of 45%.

According to table 3.7. of the Guidance on the Application of the CLP criteria this indicates a **moderate sensitizer** (Concentration for intradermal induction (%w/v) > 1.0, Incidence sensitized guinea pigs (%) ≥ 30, **Skin Sens 1 B**).

Buehler Method

No reaction was seen at any test or naive control site following challenge. The positive control data confirmed the validity of this test system.

The Buehler Method indicates no sensitization potential.

Summary Non-human data

The non-human data demonstrates that BIT is a moderate sensitizer according to the criteria set out in the CLP guidance. Thus, a generic concentration limit of 1% (10.000 ppm) would apply according to table 3.9.

Human data

In the HRIPT no reactions to BIT occurred at 360 ppm, while 9% of volunteers reacted at 725 ppm. According to the Guidance on the Application of the CLP criteria HRIPT is not a clinical study and is only of historical relevance. Nevertheless, the HRIPT results indicate that the SCL can be set above 360 ppm and below 725 ppm. There is also a possibility of false positives as irritation effects have been observed above 500 ppm.

The diagnostic patch tests show results on patients with dermatitis and could indicate the elicitation threshold for BIT. The results cannot be used for finding the induction threshold relevant for assigning an SCL. It may be worth noting that the BIT concentrations used in the diagnostic patch testing where relatively high considering the concentrations used in the HRIPT study above.

[7] Guidance on the Application of the CLP Criteria, Version 5.0, Section 3.4.2.2

Additional Studies

There is a report indicating that BIT caused skin allergies from PVC gloves containing 20-30 ppm of BIT.[8] The study investigated contact allergy to plastic gloves, which is found as a rare phenomenon. The authors suspect delayed-type contact allergy to benzisothiazolinone from polyvinyl chloride (PVC) gloves. To find relevant cases, they looked through their medical records from 1991 to 2005. The study identified a total of 8 patients who are allergic to benzisothiazolinone and who had experienced exacerbations of their hand dermatitis while using PVC gloves. Patch testing showed that 3 of them had weak allergic or doubtful reactions to the material of the glove. Six of them had used products, which in chemical analysis were shown to contain 9 to 32 ppm of benzisothiazolinone. All patients had displayed hand dermatitis for years and as BIT is an irritant the authors state that the possibility of false-positive reactions to BIT cannot be excluded in the present series of patients. The authors conclude that to their knowledge, there have been no previous reports of contact allergy to antimicrobial agents in plastic gloves. They also conclude that small amounts of benzisothiazolinone in the gloves may sensitize those who already have hand dermatitis. However, these findings in those *who already have hand dermatitis* only are likely to be due to elicitation or irritant effects. Furthermore, from January 1991 to September 2005, BIT was tested on a total of 2264 patients, and 17 (0.75%) of them had an allergic reaction to it. This means a rather low incidence and would support Skin Sens 1B.

The sensitization threshold (i. e. the elicitation threshold for provoking an effect on the skin) for patients with an existing hand dermatitis is not relevant for the setting of the SCL under CLP (SCL is set for induction of sensitization). Furthermore, as detailed out above, such human case studies cannot be validated, lack details, do not show dose-response and can hence only be considered “as supporting additional evidence”.

Summary of the toxicological data for setting the SCL

The Guidance on the Application of the CLP criteria (version 5.0, chapter 3.4.2.5) states: “*SCLs shall be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the GCL for classification. As such the recommended SCL should normally be as given in Table 3.9 (chapter 3.4.2.5 page 348). However, supported by reliable data the SCL could have some other value below the GCL. Reliable data could be human data from e. g. workplace studies where the exposure is defined*.”

Following the guidance, the toxicological data clearly demonstrates that BIT is a moderate sensitizer. According to table 3.9 an SCL for a moderate sensitizer should be between 1000 and 10,000 ppm. The currently available robust and guidance-based data clearly supports the dossier submitter’s proposal. The available data would even allow for setting a higher SCL, i.e. the CLH submitter's proposal of 500 ppm is sufficiently conservative.

General aspects of sensitizing preservatives

Since biocides for in-can applications are intended to destroy all available micro-organisms, it is difficult to imagine that such a substance will have absolutely no risk factors. In general, the risk depends on two factors: the hazard (e. g. the toxicity) and the exposure. Of course, it is the aim of the industry to use substances which are as less hazardous as possible and to use

[8] Aalto-Korte K, Alanko K, Henriks-Eckerman ML, Jolanki R. 2006. Antimicrobial allergy from polyvinyl chloride gloves. Arch Dermatol 142: 1326–1330

them at concentrations as low as possible while still being effective. Using biocides at too high concentrations not only increases the intrinsic hazard properties of a product but it also increases costs and is thus avoided.

Isothiazolinones have been under discussion in Germany due to an increased number of persons being allergic to Methylisothiazolinone (MIT). However, this increase can be mainly attributed to the use in cosmetics. For a long time 100 ppm of MIT in cosmetics, even in leave-on products (e.g. skin lotions), was permitted. However, in the current version of the regulation (EC) No. 1223/2009 the limit values have been lowered and the use is only allowed for "rinse off" products at concentrations below 15 ppm. Due to the regulatory restrictions and the efforts of the cosmetics industry, the quantities used in cosmetics have been substantially reduced and this has resulted in a clear reduction of prevalence rate with sensitization to MIT.[9] This decrease is also observed in other European countries.[10]

According to our knowledge, sensitizations to BIT has never been a relevant epidemiologic issue in the general public. This is due to its much lower sensitization potency and the low volatility. In fact, it has been suggested by leading dermatologists that the paint and coatings industry should use BIT rather than MIT or C(M)IT/MIT.[11] However, this is not possible, if the SCLs of the different isothiazolinones do not reflect the different potency. As the substances with the higher potency also feature a higher efficacy and are thus usable in lower concentrations, the levelling of the SCLs provides an incentive to use the more potent sensitizers, which is not in line with consumer protection.

Conclusion

VdL supports the proposal of the dossier submitter to keep the current SCL of 500 ppm for skin sensitization for BIT, which is well supported by the available toxicological data. Furthermore, this is also justified when compared with the other isothiazolinones' relative sensitization potential. Setting the same SCL for BIT as for the other classified isothiazolinones is neither toxicologically justified, nor will it lead to an improved consumer protection. Hence, VdL proposes to follow the proposal detailed out in the CLH dossier prepared by the Spanish authority.

The German paint and printing ink association (VdL) represents roughly 200 – mostly mid-sized – manufacturers of paints, coatings and printing inks. The VdL stands for nearly 90 percent of this industry in Germany. In 2019 the German manufacturers of paints, coatings and printing inks realized sales of ca. 8 billion euros and employed ca. 25,000 staff.

[9] https://www.bfr.bund.de/cm/343/21-sitzung-der-bfr-kommission-fuer-kosmetische-mittel.pdf
[10] Matellanes-Palacios et al, Contact Dermatitis. 2020, doi: 10.1111/cod.13591
[11] UBA Fachgespräch „Sensibilisierende Wirkung von Konservierungsmitteln in Bautenfarben – Verbraucherinformationen und Alternativen" 2017