Comments on "Annex XV - Identification of UV-326 and UV-329 as SVHCs"

10 October 2023

The members of the European Light Stabilisers and Antioxidants Association (ELiSANA), a Sector Group of Cefic, are pleased to provide scientific comments on the annex XV SVHC proposal for UV-326 and UV-329.

ELiSANA agrees and supports the SVHC proposal for UV-326 given that its vB properties were confirmed by the results of the OECD 305 study conducted by the Lead Registrant.

However, we respectfully disagree with the SVHC proposal for UV-329 and with its B/vB identification as this conclusion contradicts the results of the OECD-conform study conducted by the Lead Registrant.

The Dossier Submitter proposes a grouping approach for UV-329 and UV-P. However, for UV-P additionally toxicokinetic data (rats) and new human biomonitoring data are available showing it is not likely to bioaccumulate. Therefore, ELiSANA understands that the conclusion should then be that UV-329 is also not likely to bioaccumulate.

Kind regards,

Marta Siddu, ELiSANA Sector Group Manager

European Chemical Industry Council - Cefic
Rue Belliard 40, 1040 Brussels, Belgium
Tel. +32.470.244.778
msi@cefic.be
www.cefic.org
http://elisana.cefic.org/

ABOUT ELiSANA

The European Light Stabilisers and Antioxidants Association (ELiSANA), a sector group of Cefic, was created in 2004 with the mission to become the trusted reference on health, safety and environmental information related to antioxidants and UV light stabilisers.

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ELiSANA
Rue Belliard 40, Box 15, B-1040 Brussels
msi@cefic.be | www.elisana.cefic.org
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Conclusion

- Bioaccumulation in fish is still the preferred endpoint under the current REACH legislation.
- A valid GLP guideline study on the bioconcentration in fish (aqueous exposure) is available.
- The experimentally determined BCF values in fish are < 2000 L/kg (max. BCF = 461 L/kg).
- Prediction of BCF with complex QSAR model OASIS Catalogic BCF baseline v05.12: BCF = 115 ± 3 L/kg (BASF SE, 2022c; completely in parametric and mechanistic applicability domain; all relevant structures within AD (89% of total structures)).
- According to the benchmarking method (Brooke & Crookes, 2012), UV-329 is not vB.
- German CA suggests grouping approach for UV-329 and UV-P. Toxicokinetic data (rats) and human biomonitoring for UV-P show that it is not likely to bioaccumulate. Therefore, the conclusion of German CA should be that also UV-329 is not likely to bioaccumulate.
- Prediction of BCF via OECD BCF Estimation Tool not applicable as BCF has already been experimentally determined. Applicability domain not thoroughly checked by eMSCA.
- HYBIT study:
    - Not valid as test concentrations were not maintained.
    - Not reliable: no reliable explanation for differences between structurally similar substances and strong deviation between fish BCF and HYBIT BCF.
    - Non-GLP, nonstandard, poor reporting.

Summary

- The fish bioaccumulation study on UV-329 meets all requirements as described within the OECD TG 305 and is therefore considered as reliable without restrictions (Klimisch 1).
- Thus, the experimentally derived BCF values (**max. BCF = 461 L/kg**) reveal that UV-329 is clearly below the threshold limit value of 2000; therefore, UV-329 does not meet the criteria for B/vB.
- Further data support this assessment:
    - Benchmarking via depuration rate: experimentally determined k_2 higher than critical values for vB substances: not vB.
    - QSAR data: the OASIS CATALOGIC v.5.15.2.14 BCF baseline model v.05.12 considers relevant mitigating factors such as metabolism, water solubility and molecular size to refine a log Kow based BCF_{max} (BCF_{max} = 27040 L/kg): **$BCF_{corrected}$ = 115 ± 3 L/kg.**
    - Toxicokinetic data: toxicokinetic studies with the structurally similar substance UV-P
        - Oral administration in rat: substance rapidly taken up, rapidly metabolized by liver, and excreted via the kidney; 91% eliminated from body after 2 days.
        - Oral administration in humans: 69% excreted via the kidney, 25% excreted through the feces.
- On the contrary, the calculations and reassessments by the eMSCA lack appropriate documentation (justifications, descriptions of applicability domains and robustness).
    - Fish bioaccumulation study with UV-329: the BoxCox-transformed k_2 value derived by the eMSCA cannot be accepted as a better fit has neither been demonstrated nor justified.
    - OECD BCF Estimation Tool:

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- The tool is intended for the estimation of a BCF from the k_2 of a dietary biomagnification study, but not for aqueous exposure studies.
- BCFs predicted without justification and thorough check of method (suitability, applicability domain).
- As an experimentally derived BCF is available, there is no need for the application of this tool.
- Use and applicability of methods not sufficiently justified by the eMSCA.

- HYBIT study: the study does not meet the validity criteria, i.e., maintaining exposure concentration. Other validity criteria which allow for such a deviation were not published. The HYBIT guideline is not yet approved, and the study as such was conducted as non-GLP. *Hyalella* BCF values were extremely high compared to fish BCF and thus overestimates the bioaccumulation potential as known from fish. The comparability of fish BCF (regulatory values) and *Hyalella* BCF are not yet established. Significant differences in BCF values from HYBIT studies between structurally similar substances.
- Weight-of-evidence approach: the highest weight is given to the (invalid) HYBIT study; valid fish BCF study not considered adequately.
- The German CA suggests grouping approach for UV-329 and UV-P, however toxicokinetic data (rats) and human biomonitoring for UV-P show that it is not likely to bioaccumulate.
- Therefore, the conclusion of German CA should be that also UV-329 is not likely to bioaccumulate.

3.4 Bioaccumulation

3.4.1.2.3.1 Robust Study Summaries of Key Studies: OECD TG 305 with UV-329 (aqueous exposure)

- Results from study report (BASF SE, 2017):
  - Steady state BCF: **BCF_{SSL} = 461 L/kg**
  - Kinetic BCF:
    - k_g = 0.0132 d^{-1}
    - One-compartment model:
      - **BCF_{K1Lg} = 361 L/kg**
        - k_1 = 49.8 L/kg/d
        - k_{2g} = 0.168 d^{-1} (k_2 = 0.182 d^{-1})
    - Two-compartment model:
      - **BCF_{K2Lg} = 458 L/kg**
        - k_{12} = 64.14 L/kg/d
        - k_{23g} = 0.2672 d^{-1}

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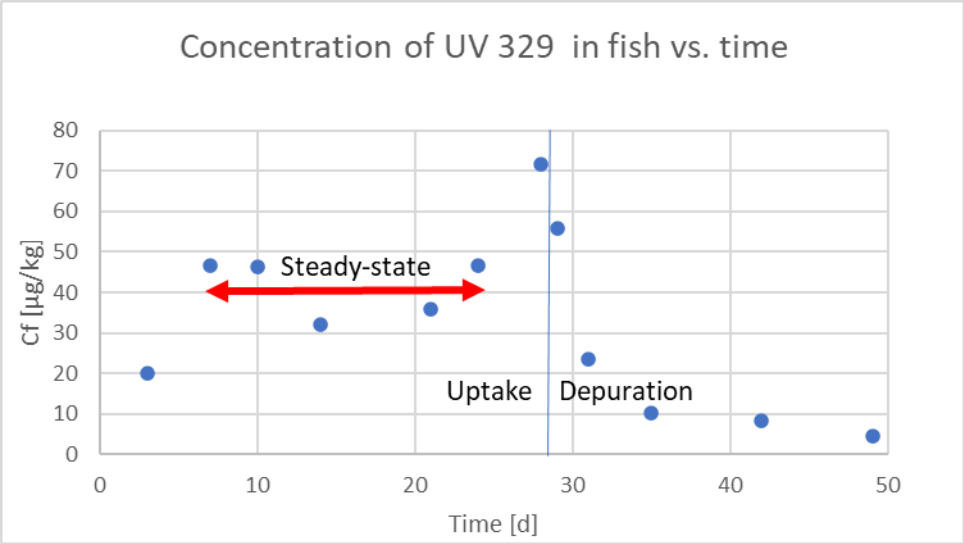

Figure 1: Plot of the concentration in whole fish (C_f) vs. time

- Results from QSAR (OASIS Catalogic BCF baseline model v.05.12; BASF SE, 2022c)
  - **$BCF_{corrected}$ = 115 ± 3 L/kg** (100 % within the applicability domain of the model)
  - Effect of relevant mitigating factors to refine BCF_{max} = 27040 L/kg:
    - Metabolism: 0.77
    - Molecular size: 0.23
    - Water solubility: 2.11E-05
  - See Annex 1 for further information regarding model and calculation (QMRF and QPRF).

- <u>Steady state achieved?</u>
  The concentration in fish (C_f) were within ±20% of each other from days 7 to 24 of the uptake period. It was therefore assumed that steady state was achieved according to the criteria of OECD TG 305 (Figure 1). The C_f on day 28 was 53% higher than the concentration of the previous measurement on day 24. The fish samples of day 28 had a higher lipid content but not extremely high enough to explain the increase. The concentration in water was stable over the uptake period (except for day 7). Therefore, no explanation could be given for the final increase in C_f. As it is not expected that there would have been a further increase in C_f since the concentration in fish were stable over the previous period between day 7 and 24. In order to derive a conservative (worst-case) BCF, the high C_f of day 28 was used for the calculation of the BCF_{SS}. The resulting BCF_{SSL} 461 L/kg. This value was not accepted by the eMSCA.
  However, the obtained BCF_{SSL}, which was clearly below the critical threshold for bioaccumulation (B), is further supported by the results from a non-GLP preliminary test revealing a BCF_K of 56 (Figure 2). The preliminary test was performed prior to the final study and the data are reported within the study report of BASF SE (2017).

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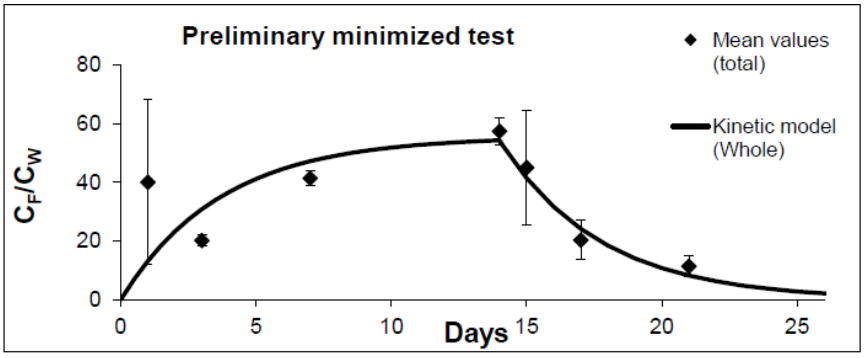

Summarized values from preliminary test[a]:

C_W mean aqueous concentration, filtered (µg/L) (mean (days 0 – 14) ± standard deviation)	0.18 ± *0.017*
Uptake rate constant, k_1 (d^{-1}) (95% confidence interval)	15.0 (6.3-23.6)
Depuration rate constant, k_2 (d^{-1}) (95% confidence interval)	0.27 (0.10-0.44)
$t_{1/2}$, (depuration half-life, days)	2.6
$BCF_k = k_1/k_2$	56

Figure 2: Data on preliminary minimized bioconcentration test with UV-329 (p. 23 of original report; BASF SE, 2017)

- The alternatively calculated kinetic BCF (BCF_{KLg} = 361 and 458 L/kg, one- and two-compartment model), which is also accepted for the assessment of the bioaccumulation potential by ECHA, is also not accepted by the eMSCA. The eMSCA arguments that there were "experimental artefacts" due to "problems maintaining solute concentration." However, the test concentrations were stable within the uptake period, not exceeding the allowed range of ±20%. Only on day 7, the concentration in water dropped significantly due to a technical malfunctioning of the metering pump. This drop lasted only for a short period of time (<< 24 h) as shown by regular water samples and additional function control samples (Figure 3). The system was fixed within the same day. The drop was detected at 9:45 am and set to the correct concentration by 11:00 am. The concentration in fish on day 7 and 10 were almost identical; therefore, it can be concluded that this very short concentration (C_w) decrease did not lead to a significant decrease in C_f. The "drop" in C_f from day 10 to 14 by approximately 30% would be a rather late reaction to this failure; especially as the treatment concentration was properly maintained for the uptake period with the exception on day 7.
  As there is sufficient evidence that the test concentrations were maintained adequately for most of the uptake period and no relevant influence of the TOC on the freely dissolved concentration of the test item (Figure 3), there is no reasoning for considering the fitted k_1 value as unreliable. The Registrant considers the k_1 value as reliable.

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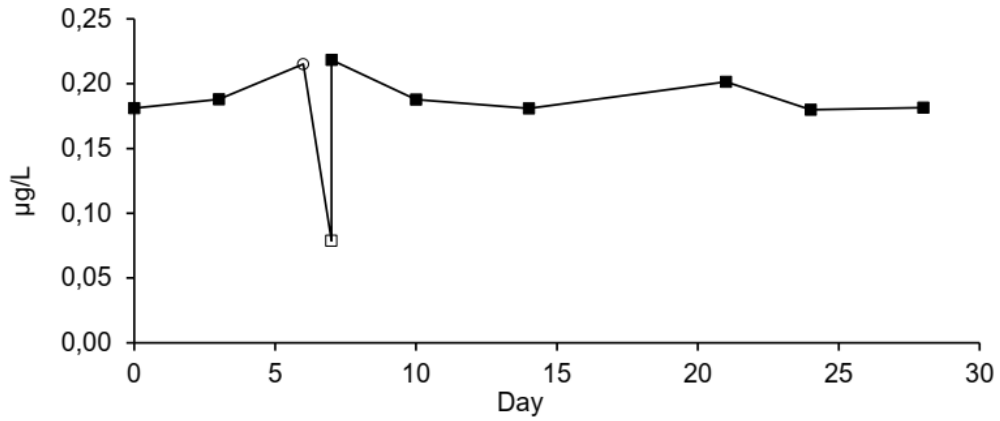

Open circle: Day 6 is only a system function control sample (see Tab 12), not included in the mean measured calculation (see chapter 3.7.1). It is included in the graph only to illustrate that the drop in test substance concentration was very brief.
Open square: Low day 7 value is not included in the mean measured calculation.

Figure 3: Plot of the measured concentrations in test solution (µg/L; Figure 2 of original report; BASF SE, 2017)

- TOC concentrations were not measured in the treatment but closely monitored in the control. The TOC values were between 0.8 and 1.8 mg/L, which is below the upper limit for the dilution water according to OECD TG 305 (TOC < 2 mg/L). The TOC is mainly influenced by the fish loading rate and feeding. As the test conditions in control and treatment were identical with respect to
    - tank volume: 100 L,
    - biomass loading rate: 0.31 g/L/d (OECD TG 305: 0.1 to 1.0 g/L/d),
    - water exchange rate: 21 L/h (504 L/d), and
    - feeding and cleaning procedures.

  As the test conditions were identical for the treatment and the control group, it can be expected that there was no significant difference of the TOC between treatment and control; therefore, the TOC was most likely below 2 mg/L similar to the control.
  TOC can reduce the freely dissolved concentration of test chemicals in water by binding to TOC; however, as the measured TOC concentrations were low, no "strong influence" as implied by the eMSCA of the TOC on the freely dissolved concentration of UV-329 is to be expected. The same is expected for any considerable influence on the bioavailability of UV-329 in this test. Further, the true dissolution of the test substance was demonstrated by analyzing centrifuged solutions prior to the start of exposure as well as by analyzing filtered versus unfiltered samples (n = 3; recovery of 94% to 99%).
  It can be concluded that the TOC concentration in the treatment group was within acceptable limits (< 2 mg/L); therefore, a significant influence on the test concentration can be excluded.
- k_2 values from the study report were accepted by the eMSCA as "reliable". However, the eMSCA derived a further k_2 value with no justification for data fitting ("one-compartment, BoxCox, best fit": k_{2g} = 0.119 d^{-1}), which was performed to derive a lower depuration rate constant than determined in the study (BASF SE, 2017).

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- As an alternative approach to the experimentally derived BCF for UV-329, the eMSCA used the OECD-BCF-Estimation Tool (Version 2) to derive the BCF based on the k_2 from the aqueous exposure bioconcentration study by BASF SE (2017). Annex 8 (Approaches to estimate tentative BCFs from data collected in the dietary exposure study) of OECD TG 305 gives a brief description of the methods as well as some of the requirements. The tool is intended for the estimation of a BCF from bioconcentration studies with dietary exposure, which results in biomagnification factors (BMF), as the BCF is needed in most regulatory contexts. The guideline does not consider the estimation of the uptake rate (k_1) or the BCF from studies with aqueous exposure. OECD TG 305 emphasizes the need for a justification of the selected method for deriving k_1 and BCF as there are certain assumptions inherent to the estimation approaches presented in the tool. One of the main aspects is the training set, which was used to develop the uptake estimation methods. Similar to other estimation methods (e.g., QSARs), the applicability domain should be carefully checked, if the substances in the training set are representative for the substance in question, as well as if other factors are applicable (e.g., log Kow and fish size). The justification by the eMSCA for the use of the methods is poor and the applicability domain was simply checked based on the log Kow and fish species. However, the log Kow range is only specified for Sijm *et al.* (1995) and was then applied on the other calculation methods.
- The OECD GD 264 [6] points out that "an estimate of uncertainties in the measured parameters used in the estimates (depuration rate constant and BMF) can be derived but estimates of uncertainty in the predicted parameters (uptake rate constant and BCF) are not possible to derive, because they are related both to the dietary study measured data and the models used in the prediction, including their underlying training sets." The Registrant is therefore of the opinion that the use of the estimation methods requires a discussion of resulting uncertainties in addition to the check for the applicability domain. It is not justified to use these estimated BCF values without detailed documentation and discussion instead of the experimentally derived BCF values from valid GLP studies which were performed according to the current OECD TG 305 test guideline and with the required standardization such as growth and lipid corrections. In addition, the eMSCA noted in the Annex XV report (p. 58, 3rd paragraph) that "these calculated BCFs may be more uncertain than experimental BCFs due to the uncertainty in the k_1 prediction." The Registrant would like to point out that no uncertainty analysis was performed by the eMSCA. It should be considered that the resulting estimated BCFs are highly uncertain and should therefore not be considered at this level.
- The Registrant does not accept the BCF values derived using the OECD BCF Estimation Tool due to insufficient documentation and justification as well as the lack of suitability of the method.
- The Registrant still regards the submitted bioconcentration study in fish with UV-329, which was performed according to the current OECD test guideline 305 and under the regulations of GLP, as acceptable. The validity criteria of OECD TG 305 were kept.

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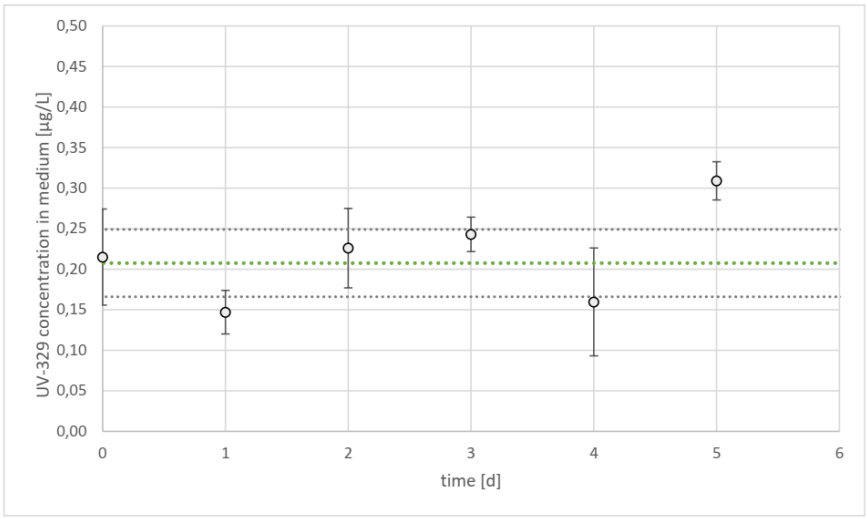
3.4.1.2.3.2 "Development of a bioaccumulation test using *Hyalella azteca*" - Bioconcentration test with UV-329

Schlechtriem *et al.* (2022) investigated the bioconcentration potential of UV-329 and UV-234 with *Hyalella azteca*. The protocol is described in Schlechtriem *et al.* (2019). Two experiments with UV-329 were performed:

- Solvent-facilitated application: the results from the solvent-facilitated application for UV-329 were disregarded due to a high mortality. In the solvent-free exposure, mortality was not reported.
- Solvent-free column-generated application.

Solvent-free column-generated application: the uptake phase was 5 days with daily measurement of the test concentration via LC-MS/MS. Figure 4 shows that the test concentrations during the uptake phase of UV-329 were not within the ±20% range of the nominal values: UV-329: 0.208 ±0.055 µg/L. Three out of six determined concentrations were out of the acceptable range. In the current draft version of the respective OECD draft guideline for the HYBIT test (Version 06.2023, revised based on EG comments 12.2022), one of the validity criteria is maintaining the test concentration at ±20% of the mean measured value.

Further validity criteria cannot be checked as information on water temperature, dissolved oxygen concentration and mortality were not reported by Schlechtriem *et al.* (2022).



*Green dotted line marks average UV-329 concentration in test medium (TWA = 0.208 µg/L); black dotted lines mark the ± 20 % concentration range considering the calculated TWA concentration. Source: Fh IME, own diagram.

Figure 4: Bioconcentration study with UV-329: medium concentration during the uptake phase (solvent-free application) (Figure 18 of Schlechtriem et al., 2022; 22)

The following lipid-corrected (3%) BCF values were reported for the solvent-free exposure:

- BCF_{SSL}: 11063 L/kg
- BCF_{KL}: 11876 L/kg
- k_1: 8288 L/kg/d
- k_2: 0.992 d^{-1}

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These BCF values are extremely high compared to the BCF values determined in fish. It should be noted that Schlechtriem *et al.* (2022), who developed and performed the *Hyalella* bioaccumulation tests, refer to a conclusion from Schlechtriem *et al.* (2019) that "BCF values calculated for *H. azteca* tend to be higher compared to fish leading to a type I error falsely inferring the existence of a high bioaccumulation potential for a chemical in fish (BCF > 2000) that is not there." It is therefore questionable if the results from the HYBIT study for UV-329 should be used for comparison with the criteria for B/vB according to Annex XII of the REACH Regulation. In case of the study with UV-329, the results should be carefully considered as

- No standardized guideline is available so far for bioaccumulation in *Hyalella azteca*.
- The documentation and reporting of the test conditions and results is not complete.
- The test concentration was not maintained within acceptable limits (±20%).
- The study was not performed according to GLP.
- A valid bioaccumulation study in fish is available (performed according to OECD TG 305 and under GLP).

It should also be considered that Schlechtriem *et al.* (2022) performed a HYBIT study with the benzotriazole UV-234, which is part of the same report. The study was performed by solvent-facilitated application of the test substance. The test concentrations were satisfactorily maintained at ±20% of the mean value (TWA = 0.997 µg/L). The BCF values for UV-234 and UV-329 are summarized in the table below taken from the report by Schlechtriem *et al.* (2022). Although UV-234 and UV-329 are structurally similar substances, the BCF values resulting from the HYBIT tests show a large difference between both substances. The solvent used in the experiment with UV-234 should not have reduced the bioaccumulation as seen in the extremely high BCF values of the solvent-based test with UV-329 (which was disregarded due to the high mortality). It seems that the applied HYBIT method might not be sufficiently reliable for the determination of the bioconcentration factors of superhydrophobic substances such as the benzotriazoles.

Table 1: Results of the bioconcentration tests with solvent-facilitated and solvent-free application of UV-234 and UV-329 (BCF values are normalized to 5% lipid content instead of 3%; Table 5 of Schlechtriem et al., 2022)

Substance	Solvent	Target conc. [µg/L]	TWA [µg/L]	k_1 [L/kg/day]	k_2 [1/d]	BCF_k [L/kg]	BCF_{kL} [L/kg]	BCF_{ss} [L/kg]	BCF_{ssL} [L/kg]
UV-234	x	1µg/L	0.997	198	0.273	725	1,502	485	1,005
UV-329*	x	1µg/L	0.0779	66,085	0.657	100,601	208,415	90,043	186,542
UV-329			0.208	8,288	0.992	8,352	19,842	7,744	18,397

The high bioaccumulation in *Hyalella* compared to the results for fish might be partly explained by a difference in the metabolism of the organisms. The draft PBT guidance states that "*H. azteca* has the ability to metabolise substances, but the biotransformation reactions can be different from fish species

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Rue Belliard 40, Box 15, B-1040 Brussels
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(Fu et al, 2021; Kosfeld *et al.*, 2020). A Comparison between the metabolic rate of *H. azteca* with fish *in vitro* has shown that fish tend to have higher metabolic activity (Kosfeld *et al.*, 2020). Since metabolism rates influence the BCF, this may explain why *H. azteca* tends to have higher BCFs than fish when normalized to a default 5% lipid content (Schlechtriem *et al.*, 2019).

Goss & Ebert (2023) consider that metabolism was dominating in the HYBIT test with UV-234, as they could not model k_2 and BCF for the substance. Based on the chemical structure of UV-234 and UV-329, it is unexpected that metabolism would be dominating in the bioconcentration study with UV-234, but not in the study with UV-329. In the structure of UV-234, the hydroxy group is hindered by an alkyl group in ortho position, while in UV-329 this hydroxy group is freely accessible. Based on the current experience with the HYBIT method, it cannot be concluded which test result is more plausible. Therefore, the BCF values derived for UV-329 should be considered as not reliable or at least as questionable.

Metabolism is an accepted mitigating factor in bioaccumulation processes in organisms. If this process is not relevant in the HYBIT studies, the bioaccumulation potential will be overrated for other organisms than *Hyalella azteca*. The Registrant is of the opinion that the aspect of metabolism as a mitigating factor for bioaccumulation in organisms has not been carefully considered by the eMSCA. The methods included in the OECD BCF Estimation Tool do not take any mitigating factors into account when calculating BCF values. The Registrant has performed BCF calculations using the BCF baseline model v.05.12 of OASIS CATALOGIC v.5.15.2.14 (BASF SE, 2022a-c, d). The metabolism had the highest mitigating effect on the bioaccumulation potential of the substances (UV-329, UV-P, and UV-234). UV-P and UV-329 have a higher mitigating potential of metabolism than UV-234, but the differences are rather small. UV-234 is completely within the applicability domain. UV-329 and UV-P were within the structural domain with >80 % due to unknown and/or incorrectly predicted fragments in the structural domain. For details, please refer to Table 2 and Annex 1.

The Registrant does not follow the considerations of the eMSCA regarding the report by Goss & Ebert (2023) and the HYBIT results. It is stated that “the experimentally measured k_1 in *Hyalella azteca* are quite plausible due to the fact that DOC concentration of 1 mg/L is very low and well within the accepted limits […] The […] derived k_1 are therefore plausible”. However, a few lines below, the eMSCA states that “it can be assumed that the major part of UV-234 is bound to DOC if aqueous exposure is used and the subsequently derived k_1 values need to be disregarded in a regulatory assessment.” The eMSCA considers the test results plausible but in case of UV-234 this statement is not further considered as the uptake rate should be disregarded. The chemical analysis of the water phase showed stable concentrations of the test substance in case of UV-234. As described by Schlechtriem *et al.* (2022), biofilms were growing in the experimental setup for UV-234. The substance could have been partly adsorbed to this matrix; however, as mentioned earlier the test animals were feeding on these biofilms, which would have resulted in additional dietary uptake of the substance.

The Registrant does not agree with the conclusions of the eMSCA on the HYBIT testing on UV-329 and UV-234. The eMSCA accepts the BCF values of > 5000 L/kg for UV-329, while the results for UV-234 (BCF < 2000 L/kg) are rejected. As the eMSCA assumes similar properties for both substances regarding the bioaccumulation potential, the Registrant is not able to comprehend this conclusion. Both substances have a high log Kow and a very low water solubility, the experimental problems should have been similar in both cases. However, the eMSCA rejects a study which showed steady-state conditions in the tissue concentrations as well as stable concentrations in water, while it accepts the

ELiSANA
Rue Belliard 40, Box 15, B-1040 Brussels
msi@cefic.be | www.elisana.cefic.org
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results for UV-329 with no steady state and a high depuration rate constant, which contrasts with the cited k_2 values for other very bioaccumulative substances.

The eMSCA adopted the summary of a project report by Goss & Ebert (2023). The authors state that "data in the superhydrophobic range are too sparse and Kow uncertainties too high to conclusively validate the prediction method or the experimental data." The Registrant would like to point out that the results from the HYBIT tests should therefore be considered with caution.

In the Annex XV report, it is stated that "According to the draft PBT guidance, BCFs from *H. azteca* bioconcentration tests can be compared against the REACH Annex XIII criteria on B and vB properties." However, fish is still the preferred test organism in the current REACH legislation as well as in the latest version of the REACH draft PBT guidance (R.11, version 4.0, 06 September 2023; ECHA, 2023). In addition, the significant different BCF values for the structurally similar substances UV-234 and UV-329 in the same test system could not be reliably explained. As a valid fish study is available, which was performed according to an approved OECD guideline and under the conditions of Good Laboratory Practice (GLP) as required for new data under REACH, this study should be preferred in the assessment of the bioaccumulation potential and at least given significantly more weight than the HYBIT test in the weight-of-evidence approach of the Annex XV dossier.

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Table 2: BCF calculation via the CATALOGIC BCF Baseline model v.05.12 (3, 4, 5; see QMRF and QPRF in Annex 1 for details)

Common name		**UV-329**	**UV-P**	**UV-234**
CAS No.		3147-75-9	2440-22-4	70321-86-7
log P_{ow}		6.21	3	7.67
Molecular weight [Da]		323.4	225.2	447.5
Water solubility (FR) [mg/L]		0.1678	25.59	0.001648
BCF corrected [L/kg]		115 ± 3	10 ± 1	44 ± 3
log BCF corrected [log(L/kg) wet]		2.06	0.99	1.64
log BCFmax		4.432	2.2602	4.141
Relative mitigating effect of **Acids**		0	0	0
Relative mitigating effect of **Metabolism**		0.7743	0.8	0.7313
Relative mitigating effect of **Phenols**		0	0	0
Relative mitigating effect of **Size**		0.23113	0.18325	0.2895
Relative mitigating effect of **Water solubility**		2.11E-05	7.79E-03	2.94E-05
Diameter Max: Min [Å]		14.6	13.4	15.6
Diameter Max: Max [Å]		17.4	13.5	17.7
Diameter Max: Average [Å]		15.8	13.4	16.9
Applicability domain:				
Parameter ranges		In	In	In
Structural domain	Correct and additional fragments Structural domain	89.47%	83.33%	100.00%
	Incorrect fragments Structural domain	5.26%	16.67%	0.00%
	Unknown fragments Structural domain	5.26%	0.00%	0.00%
	Total Structural domain	Out	Out	In
Mechanistic domain		In	In	In
Total Domain		Out of Domain	Out of Domain	In Domain

In addition to lacking experience with the HYBIT method and superhydrophobic substances such as the benzotriazoles, there are other aspects of these data which lead to the conclusion that these results should be exempted from the bioaccumulation assessment. There are significant inconsistencies between the HYBIT studies with UV-234 and UV-329, which cannot be explained. In case of the HYBIT study with UV-329, there were problems maintaining stable solute concentrations during the uptake phase. In addition, it should be emphasized that the studies were performed without GLP and without an internationally accepted guideline. The available data do not allow to check all validity criteria of the currently discussed draft guideline.

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3.4.2.1 Bioaccumulation in terrestrial organisms (soil dwelling organisms, vertebrates): detection in breast milk

The publications presented by the eMSCA as supporting evidence in the bioaccumulation assessment should be rejected. The quality of the data is questionable. Lee *et al.* (2015) excluded samples which were associated with occupational exposure, gestational diabetes, thyroid disease, surgical disease, and congenital deformity; however, they did not check if the participants of the study used products with potential exposure to UV-326 and/or UV-329, which could have been contained in personal care products. Lee *et al.* referred to another study in which the major exposure sources for SMCs and BUVSs to lactating mothers was likely to be the use of personal care products such as hand lotion, cosmetics, shampoo, and detergent (Reiner and Kannan, 2006). Also, other previous studies have reported the significant associations between the levels of SMCs or UV filters in women's fluids and personal use of perfume and cosmetics (Lignell *et al.*, 2008; Schlumpf *et al.*, 2010; Yin *et al.*, 2012).

In addition, the average concentrations for both UV-326 as well as for UV-329 were below the LOQ of the method used in this paper. Kim *et al.* (2019) sampled breast milk from women in different settings, e.g., in Japan samples were mainly taken in urban areas, whereas in Vietnam and the Philippines samples were also taken from around waste and recycling sites. Information on use of personal care products by the women was not collected. In addition, the sample size is very small for a reliable comparison between the different regions/countries by Kim *et al.* (2019).

3.4.3 Summary and discussion on bioaccumulation: UV-329

The eMSCA is assessing the bioaccumulation potential of UV-329 following a weight-of-evidence approach. The data on the aquatic bioaccumulation potential of UV-329 are summarized in Table 36 of the Annex XV report. The "confidence/strength of evidence" as well as the "remaining uncertainty" have been given almost identical grades. Therefore, the Registrant does not agree that the eMSCA gives the highest weight to a non-standard and non-GLP study with clear restrictions in the weight-of-evidence approach to assess the bioaccumulation potential of UV-329. The decision is not sufficiently justified nor transparently laid down.

The Registrant would like to point out that the HYBIT study with UV-329 does not meet the validity criteria of the current draft guideline for the HYBIT test (OECD TG 315, draft). A valid fish bioaccumulation study is available which was performed according to current standards (OECD TG 305, GLP). The quality of the fish bioaccumulation study is questioned by the eMSCA as there was a very brief drop of the test concentrations in the water phase (<< 24 h); however, the test concentration in the HYBIT study was outside the ±20% range in three out of six samples. Although maintaining a stable exposure concentration is one of the validity criteria of the HYBIT study, the eMSCA did not question the quality of the result.

The recalculation of the fish BCF values using the OECD BCF Estimation Tool does not seem appropriate to the Registrant as the methods were not developed for bioaccumulation studies with aqueous exposure, but for dietary exposure studies, which lack the regulatory important BCF values. It should also be emphasized that the applied method is not a simple recalculation of the BCF, but an estimation of the BCF based on the experimentally derived depuration rate constant. In case of the presented UV-329 fish bioaccumulation study BCF values are available and do not require recalculation or prediction. The OECD Tool lacks a well-defined applicability domain for each model. The eMSCA

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supposes that the methods are acceptable as the log Kow is within the range of one of the calculation models. However, this is an extremely limited approach, which does not check for structurally similar substances in the training or validation test sets as other QSAR tools like the CATALOGIC BCF Baseline model v.05.12 can provide. In addition, the log Kow range is a general assumption for all three methods of the tool, but not specified for each model of the tool.

It should also be noted that the discussion of the weight-of-evidence approach does not include the experimentally derived BCF values which demonstrate that UV-329 is not a B/vB substances as the BCF values were < 500 L/kg.

Further information on the bioaccumulation potential of UV-329

General comments on the usability of the OECD BCF Estimation Tool (Version 2)

The eMSCA used the OECD BCF Estimation Tool for calculating a BCF, which is based on the depuration rate constant alone independent of the experimentally determined uptake rate constant. The tool is intended for the estimation of a BCF from bioconcentration studies with dietary exposure, which results in biomagnification factors (BMF) as the BCF is required in most regulatory contexts. The OECD guideline does not consider the estimation of the uptake rate (k_1) or BCF from studies with aqueous exposure. Further settings and limitations of this tool are indicated below.

The premise of the tool and its methods is that it assumes that the depuration is independent of the uptake route. Therefore, the tool uses only the depuration rate constants k_{2g} regarding measured kinetic study data. The following experimental data are needed as well: growth rate, duration of uptake and depuration phase, and the fish lipid content. Depending on the equation used either log Kow, fish weight, or both are required for deriving the uptake rate constant k_1. While fish weight has been easily measured during the study, it may sometimes be difficult to determine a reliable and valid log Kow. In case of the phenolic benzotriazoles, this difficulty can be seen in the available range of log Kow values for the individual substances.

Three methods are included in the tool. Method 1 is the “Uptake rate constant estimation method”, which is described in Annex VIII of OECD TG 305. Thirteen different allometric regression equations and QSAR-like approaches are available for this method. The restriction of the equations is the limited information available on their applicability domain. For the equation of Sijm *et al.* (1995), a log Kow range is given (log Kow: 3.6 to 8.3), while the information on the other models is rather vague. According to §239 of OECD GD 264, the assumed applicability domain for these models can be estimated from the more detailed information included by Sijm *et al.* (1995) and the information on substance types included in Barber’s (2003) reanalysis of models. In OECD GD 264, it is concluded that this approach should be useable for aromatic hydrocarbons, those that are chloro-, bromo-, nitro-substituted, and may be suitable for organochlorine and organophosphate pesticides, triarylphosphates and alcohol ethoxylates with log Kow in the range around 3.5 – 8.5. The authors pointed out that particular care must be taken when using these equations for larger, or higher molecular weight molecules where there is an indication that uptake may be over-predicted. However, no suitable range for the molecular weight is given. Compared to other QSAR models, e.g., the different models of the CATALOGIC software suite, a well-defined applicability domain is not available.

Regarding the publication date of the equations in the OECD BCF Estimation Tool (method 1: 1980 to 2003), it can be assumed that the trainings sets have been derived from non-standardized

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bioconcentration tests, which would not fulfil the conditions of the current guidelines, e.g., OECD TG 305 adopted in October 2012 (OECD, 2012). Most likely the data are problematic regarding maintaining stable exposure concentrations, distinguishing between dissolved and adsorbed fractions etc. Further, it remains unclear if the models have been validated by evaluating the equations with independent datasets.

The OECD GD 264 (OECD, 2017) points out that "an estimate of uncertainties in the measured parameters used in the estimates (depuration rate constant and BMF) can be derived but estimates of uncertainty in the predicted parameters (uptake rate constant and BCF) are not possible to derive, because they are related both to the dietary study measured data and the models used in the prediction, including their underlying training sets." The Registrant is therefore of the opinion that the use of the estimation methods requires a discussion of resulting uncertainties in addition to the check for the applicability domain. It is not justified to use these estimated BCF values instead of the experimentally derived BCF values from GLP studies which were performed according to the current OECD 305 test guideline and with the required standardization such as growth and lipid corrections without detailed documentation and discussion. If the estimated BCF values are close to or just above a critical BCF level, i.e., 2000 L/kg or 5000 L/kg, a scientific evaluation of the bioaccumulation potential and its reliability based on the uncertainties of the predicted BCF cannot be performed.

Annex VIII of OECD TG 305 refers to the review of Brooke and Crookes (2012). The authors state that "no one method is more correct than the others." They also pointed out that a clear justification should be given for the model used. The choice of model may be influenced by the level of validation and applicability domain. However, as information on validation and applicability domain are missing, this step is not practicable. For the prediction of a BCF it is not appropriate to take the mean value from all estimates derived in different ways. The evaluation should be performed as a weight-of-evidence approach including the k_1 estimate, the estimated BCF, the experimentally derived BMF, and other substance parameters (e.g., log Kow). In case of the applied calculations performed by the eMSCA, the experimentally determined BCF should have been considered as well, especially as the studies fulfill the validity criteria of OECD TG 305.

The eMSCA applied the tool without a justification for the usability and reliability of the models. The assessment of the applicability domain for the individual models is very brief and solely based on the log Kow. The eMSCA used all available methods without a further evaluation or comparison of the results. The Registrant does not agree with this approach.

Environment Agency (2012). Depuration rate constant: growth correction and use as an indicator of bioaccumulation potential

The British Environment Agency (Brooke & Crookes, 2012) developed a method for the use of the depuration rate constant as a direct measure of bioaccumulation and an alternative metric for indirect comparison against regulatory criteria for bioaccumulative (B) or very bioaccumulative (vB) substances. According to the report, very bioaccumulative substances have a depuration rate constant (k_2) of ≤ 0.085 day^{-1} in case of uncorrected BCF. For lipid-normalized BCF values ≥ 5000, the depuration rate constant (k_2) would be ≤ 0.065 day^{-1} or ≤ 0.085 day^{-1} for the lipid-normalized k_2. The critical values are summarized in Table 3. Growth-corrected BCF or depuration rate constants are not considered. The fish bioaccumulation study (BASF SE, 2017) resulted in an uncorrected k_2 of 0.182 d^{-1}. With lipid-

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normalization the corresponding k_{2L} is 0.149 d^{-1}. based on the one-compartment model parameters. The (overall) depuration rate constants from the two-compartment model are as follows for UV-329: k_{21} = 0.267 d^{-1} and k_{21L} = 0.219 d^{-1}. As the Environment Agency (Brooke & Crookes, 2012) did not provide depuration rate constants which were corrected for growth, these values for UV-329 from the study report are not considered in this evaluation.

Comparing the experimentally derived depuration rate constants of UV-329 with the critical values taken from Brooke and Crookes (2012), there is no evidence for UV-329 being considered as B or vB. In case of the not corrected depuration rate constants from the one- and the two-compartment model, the critical values are lower than the values from the study; therefore, there is no indication for the substances being assessed as B or vB. In case of the lipid-normalized depuration rate constants from Brooke & Crookes (2012), the depuration rate constant of the two-compartment model is clearly above the critical values of the Environment Agency report (Brooke & Crookes, 2012). However, the lipid-normalized depuration rate constant of the one-compartment model is below the critical value for B substance, but not for vB substances. Nevertheless, the study director chose the two-compartment model as best fit for the available bioaccumulation data in fish, which should therefore be given a higher weight in the evaluation.

The eMSCA derived a growth-corrected depuration rate constant, which is not adequate for the comparison with the available critical values. However, the Registrant calculated the corresponding uncorrected and lipid-normalized depuration rate constants (k_{2g} = 0.119 d^{-1}; k_2 = 0.132 d^{-1}; k_{2L} = 0.108 d^{-1}). The k_2 and the k_{2L} are both below the critical values for B substances, but not for vB substances.

It can be concluded that based on the experimentally derived depuration rate constants, UV-329 is clearly assessed to be not vB.

Table 3: Critical values of depuration rate constants for B/vB substances (A: one-compartment model; B: two-compartment mode; C: BoxCox-transformed data from Annex XV reportl)

	B: **≥ 2,000 L/kg**	**vB:** **≥ 5,000 L/kg**	**UV-329**
BCF (not corrected): k_2 (not corrected)	$k_2 \leq 0.178$ d^{-1}	$k_2 \leq 0.085$ d^{-1}	A: k_2 = 0.182 d^{-1} B: k_{21} = 0.219 d^{-1} C: k_2 = 0.132 d^{-1}
BCF (lipid-normalized): k_2 (not corrected)	$k_2 \leq 0.141$ d^{-1}	$k_2 \leq 0.065$ d^{-1}	
BCF (lipid-normalized): k_2 (lipid–normalized)	$k_2 \leq 0.181$ d^{-1}	$k_2 \leq 0.085$ d^{-1}	A: k_{2L} = 0.167 d^{-1} B: k_{21L} = 0.219 d^{-1} C: k_{2L} = 0.108 d^{-1}

Comparison with the structurally related benzotriazole UV-P (CAS 2440-22-4)

UV-329 and UV-P are structurally related. The hydroxyl group and the alkyl substituents are in a similar position. No additional substituents are on ortho position to the hydroxyl group, which is considered as a functional group relevant for successful and rapid conjugation through glucuronosyltransferases (Marquardt & Schäfer, 2003).

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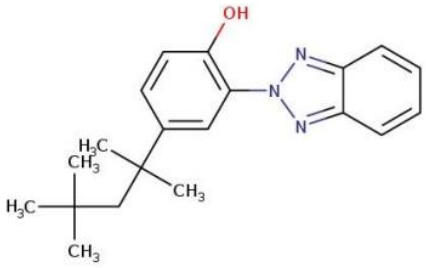
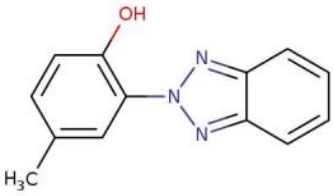
- UV-329:



- UV-P (CAS 2440-22-4):



The Annex XV report states: "The main structural difference of UV-329 to the confirmed vPvB benzotriazoles is the lack of a substituent in ortho-position to the hydroxyl group. UV-P is another phenolic benzotriazole that shares this structural feature with UV-329. However, while the substituent in para position to the hydroxy group is a *tert*-octyl group for UV-329, it is a methyl group for UV-P. Thus, UV-P is less lipophilic than UV-329 and has a higher water solubility. It is expected to be adsorptive, but to a lesser extent than UV-329. […] In summary, bioavailability is expected to be slightly higher for UV-P than for UV-329." UV-P is not a B/vB substance with experimentally determined BCF values below 2000 (BCF_{KLg} = 1471 L/kg; BCF_{SSL} = 1621 L/kg; BASF SE, 2020); therefore, following the expectation of the Annex XV report and the high structural similarity, a BCF > 5000 L/kg is not to be expected.

For a further aspect in the assessment of the bioaccumulation potential the Registrant would like to present toxicokinetic data for UV-P, which is structurally similar to UV-329 as accepted by the eMSCA (Annex XV report, p. 22–24). Two studies with rats are available which are suitable for an insight into metabolism and elimination of the substance: Ciba-Geigy Ltd. (1977a) and Ciba-Geigy Ltd. (1977b). One study investigated the effects of UV-P on the hepatic xenobiotic metabolization enzymes in the rat. The other study focused on the distribution and elimination of UV-P in the rat. In both studies the substance was administered via oral gavage. Details of these studies are given in Annex 3 to these comments. The following conclusions can be drawn from these toxicokinetic studies:

- UV-P is rapidly taken up after oral administration, rapidly metabolized by the liver and excreted via the kidney after oral administration.
- 91% of a single UV-P dose administered was eliminated from the body within 2 days (94% after 7 days).
- After single administration, 69% of the dose is excreted via the kidney and 25% is excreted through the feces.

The toxicokinetic behaviour of UV-P after oral application were also investigated in humans (Fischer *et al.*, 2023a, b). The analysis of blood and urine samples demonstrate a fast resorption of UV-P with a maximal blood level after 4 to 5 h and a maximal elimination (> 95%) via the urine within 24 hours after application. The elimination of UV-P is markedly different from benzotriazoles with substituents in

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ortho position (i.e., UV-327 and UV-328) e.g., the renal excretion rate is 2896 ± 885 µg/h for UV-P and only 0.026 ±0.007 µg/h for UV-327 and 0.013 ± 0.003 µg/h for UV-328.

As UV-P and UV-329 are structurally similar substances, it can be concluded that UV-P and UV-329 would have also similar metabolic transformation rates, concluding that both substances are not likely to bioaccumulate in both rats and humans.

Summary

- The fish bioaccumulation study on UV-329 meets all requirements as described within the OECD TG 305 and is therefore considered as reliable without restrictions (Klimisch 1).
- Thus, the experimentally derived BCF values (**max. BCF = 461 L/kg**) reveal that UV-329 is clearly below the threshold limit value of 2000; therefore, UV-329 does not meet the criteria for B/vB.
- Further data support this assessment:
    - Benchmarking via depuration rate: experimentally determined k_2 higher than critical values for vB substances: not vB.
    - QSAR data: the OASIS Catalogic v.5.15.2.14 BCF baseline model v.05.12 considers relevant mitigating factors such as metabolism, water solubility and molecular size to refine a log Kow based BCF_{max} (BCF_{max} = 27040 L/kg): **$BCF_{corrected}$ = 115 ± 3 L/kg.**
    - Toxicokinetic data: toxicokinetic studies with the structurally similar substance UV-P
        - oral administration in rat: substance rapidly taken up, rapidly metabolized by liver, and excreted via the kidney; 91% eliminated from body after 2 days.
        - oral administration in humans: 69% excreted via the kidney, 25% excreted through the feces.
- On the contrary, the calculations and reassessments by the eMSCA lack appropriate documentation (justifications, descriptions of applicability domains and robustness).
    - Fish bioaccumulation study with UV-329: the BoxCox-transformed k_2 value derived by the eMSCA cannot be accepted as a better fit has neither been demonstrated nor justified.
    - OECD BCF Estimation Tool:
        - The tool is intended for the estimation of a BCF from the k_2 of a dietary biomagnification study, but not for aqueous exposure studies.
        - BCFs predicted without justification and thorough check of method (suitability, applicability domain).
        - As an experimentally derived BCF is available, there is no need for the application of this tool.
        - Use and applicability of methods not sufficiently justified by the eMSCA.
    - HYBIT study: the study does not meet the validity criteria, i.e., maintaining exposure concentration. Other criteria not published. Guideline not yet approved, non-GLP. Comparability of fish BCF (regulatory values) and *Hyalella* BCF not yet established.
    - Weight-of-evidence approach: the highest weight is given to the (invalid) HYBIT study; valid fish BCF study not considered adequately.

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ANNEX 1 – QSAR descriptions

- ELiSANA ANNEX 1a) 3147-75-9_QPRF_Catalogic Baseline-2022-03-28:
  BASF SE (2022c). OASIS Catalogic v5.15.2.14: BCF base-line model v5.12, October 2021: UV-329. Unpublished data; BASF SE, Department for Product Safety, Ludwigshafen, Germany. Date: 2022-03-28.

- ELiSANA ANNEX 1b) 2440-22-4_QPRF_Catalogic Baseline-2022-03-28:
  BASF SE (2022a). OASIS Catalogic v5.15.2.14: BCF base-line model v5.12, October 2021: UV-P. Unpublished data; BASF SE, Department for Product Safety, Ludwigshafen, Germany. Date: 2022-03-28.

- ELiSANA ANNEX 1c) 70321-86-7_QPRF_Catalogic Baseline-2022-03-28:
  BASF SE (2022b). OASIS Catalogic v5.15.2.14: BCF base-line model v5.12, October 2021: UV-234. Unpublished data; BASF SE, Department for Product Safety, Ludwigshafen, Germany. Date: 2022-03-28.

- ELiSANA ANNEX 1d) LMC QMRF BCF base-line model:
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ANNEX 3 – Human biomonitoring

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ELiSANA
Rue Belliard 40, Box 15, B-1040 Brussels
msi@cefic.be | www.elisana.cefic.org
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