Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

bentazone (ISO); 3-isopropyl-2,1,3-benzothiadiazine-4-one-2,2-dioxide

EC Number: 246-585-8
CAS Number: 25057-89-0

CLH-O-0000006912-71-01/F

Adopted

10 December 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BENTAZONE (ISO); 3-ISOPROPYL-2,1,3-BENZOTHIADIAZINE-4-ONE-2,2-DIOXIDE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: bentazone (ISO); 3-isopropyl-2,1,3-benzothiadiazine-4-one-2,2-dioxide
EC number: 246-585-8
CAS number: 25057-89-0
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
10.01.2020	France		MemberState	1
Comment received				
FR: The auto ignition temperature of 550°C (Loeffler 1994b) is for the product not for the substance. The substance bentazone has no self ignition temperature according to the RAR of the substance (Jackson, 2001)				
Dossier Submitter's Response				
Thank you for your remark. Indeed, the study of Loeffler 1994b is performed with the product and not the substance. For the active substance, the following information is presented in the RAR: - Auto ignition temperature (bentazone sodium aqueous solution 644.9 ng/L): 537 °C (Gundrum, 2012a) - Auto flammability (bentazone technical grade): No ignition below the melting point (Jackson, 2001).				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2020	Germany		MemberState	2
Comment received				
The classification with Acute Tox. 4 (H302) and Skin Sens. 1 (H317) is supported. The proposed classification with Eye Irrit. 2 (H319) cannot be assessed because this endpoint is not evaluated in the CLH report. With regard to developmental toxicity, a comment is added below.				

Dossier Submitter's Response
Thank you for your support on classification with Acute Tox. 4 (H302) and Skin Sens. 1 (H317). With regard to developmental toxicity, see the Dossier Submitters response to comment number 4.
RAC's response
Thank you for your comment.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2020	France	BASF	Company-Manufacturer	3

Comment received

1) Chapter 10.10.4, Table 16, p 22.

a) lists the two-generation study in Wistar rats with 2-5 animals/sex/dose in the first column (Doc ID 89/0068); 2-5 is a typo and should be read as 25 animals/sex/dose.

b) the teratological study Doc ID 84/066 with bentazone administration via feed is assigned as Klimisch score 3 since the route of administration (diet) and duration of treatment (post-coitum day 0-21) does not allow a comparison with other studies on teratogenicity. BASF wants to point out that Klimisch scores are ranking the reliability of a study and a score of 3 is generally assigned as "Not reliable". BASF considers this study as fully reliable (=> Klimisch Score 1) and according to Test guideline 414 that allows the use of other routes of administration with a justification. The intention of this study was to identify if fetal resorptions as seen in gavage studies would be seen with dietary administration as well. This dietary study did not lead to fetal resorptions up to the highest dose levels used. Therefore, fetal resorptions in gavage studies are likely peak plasma effects based on the rapid substance uptake and the high plasma concentrations achieved by gavage. Based on this study it can be concluded that fetal resorptions are not considered to occur under realistic exposure scenarios. Please reconsider the Klimisch score of the study.

2) Chapter 10.10.4, Table 16, p.25, Subheader "Developmental study rat (1971) – study supplementary only (Anonymous 1971, Doc ID 71/0041)"

It is worth mentioning, already in this section and not only under the Subheader "Developmental study rat (1978)", that the embryo-/fetotoxic effects seen in this study were not reproducible when the study was repeated six years later on the same species and strain and using the same dosages of the test substance (see study Doc ID 78/039). This is necessary to address the low consistency of the effect correctly. Furthermore, according to Table 16 the study is assigned to Klimisch Score 4 and should be excluded from the overall weight of evidence.

Chapter 10.10.4, Table 16, p 26, Subheader "Developmental study rat (El-Mahdi and Lofti (1988)") is of poor quality as well, shows no dose-response relationship and is of questionable reliability, especially in view of the low doses used in this study that were otherwise proven to be NOAELs. Therefore, it is correctly assigned Klimisch score 4 and excluded from risk assessment and applicability for classification purpose. Under these conditions it is misleading to finalize the summary with the authors conclusion that the study provides supplementary information about time-dependence of fetal effects.

3) Chapter 10.10.6, p.39, "Mechanism of action", the CLH-dossier implies a structural

resemblance of bentazone to warfarin. De facto the structural similarity of bentazone and warfarin is not given (AP Tanimoto score: 0.169, calculated by ChemMine Tools (http://chemmine.ucr.edu)). Furthermore, the chapter miss to mention the apparent differences with regard to blood coagulation impairment: a) Blood coagulation parameters (partial thromboplastin times (PTT) and Quick Time (QT) or prothrombin time (PT)) were investigated in 90-day studies with bentazone (Doc IDs 1987/0173 and 2011/1173365) and were shown to be not increased in females up to dose levels of 4275 ppm (~250 mg/kg bw), thereby inhibition of blood coagulation as relevant mode of action in the developmental studies can be excluded. b) Even for male rats the extent of prolongation of blood coagulation time is not comparable to the potency of warfarin, with bentazone showing a rather mild prolongation of blood coagulation, showing reversibility and was tolerated in a cancer study in rats for 24 months at dose levels up to 180 mg/kg bw compared to warfarin, which resulted in rat mortality latest after 3 weeks after feeding of low doses (0.077 mg/kg bw/day). In conclusion, a relation of bentazone to warfarin is not justified.

4) In Chapter 10.10.7, p.40, "Short summary and overall relevance of the provided information on adverse effects on development"

a) it is confusing to discuss studies independent of their reliability. Table 32 contains studies assigned to Klimisch score 3 or 4 as Doc IDs 71/0041, 78/039, and El-Mahdi and Lofti, 1988 that were mentioned to be excluded from risk assessment or use for classification purpose.

b) the last sentence in the second part would benefit from the addition that 7 losses were due to a total post-implantation loss in one female doe. The resulting sentence could be then: "Increased implantation loss was seen in one high dose rabbit study (dose 375 mg/kg bw/day; 125 implantations and 11 losses, of which 7 were due to a total post-implantation loss in one female).

5) In Chapter 10.10.8, p 42, "Comparison with the CLP criteria"

a) there is a typo (corrected in the following) in the sentence… "Maternal toxicity at the dose levels inducing an increased post-implantation loss (range 150 - 250 mg/kg bw/day) was not observed.

b) BASF is of the opinion that the study concept of the developmental toxicity studies used to discuss maternal toxicity were not designed to see the most sensitive parameters affected by bentazone (water consumption, hematology, clinical chemistry and kidney weight), but investigated the less impaired parameters food consumption and body weight. The more sensitive parameters were rather investigated in the repeated dose studies which however do not reflect the bolus administration and are likely to underestimate the effects seen after gavage. In this sense, BASF considers the dietary developmental study (Doc. No. 84/066) as crucial for classification. Based on the results of this study, a dietary exposure up to levels inducing marked maternal toxicity did not induce post-implantation losses although the dose levels were twice as high as in the main gavage study. Therefore, the most relevant route of exposure did not induce developmental effects and raises doubt about the relevance of the effect for humans. Consequently, BASF considers bentazone as borderline between category 2 and no classification. With regard to the saturation of excretion identified after bolus administration in the mechanistic study (Doc ID 2011/1262233) to start between 80 and 160 mg/kg bw/day, the toxicokinetic differences between bolus administration and

dietary exposure are considered so marked that the hazardous property will not be expressed in humans under realistic exposure scenarios.

Therefore, and in accordance with CLP 3.7.2.5.5., BASF considers that bentazone should not be classified.

Dossier Submitter's Response

1a) Thank you for your remark. The experimental groups consisted of 25 rats per sex and dose (Doc ID 89/0068).

1b) Though no specific test guideline was mentioned in the report, the study procedure of Doc ID 84/066 was, as considered in the CLH dossier and RAR, to a great extent in compliance with the demands of Directive 87/302/EEC, May 30, 1987. It is acknowledged that this study is well performed and should be considered for classification purposes.
With respect to the administration of doses, OECD TG 414 states that "*The test chemical or vehicle is usually administered orally by intubation. If another route of administration is used, the tester should provide justification and reasoning for its selection, and appropriate modifications may be necessary (10-12). The test chemical should be administered at approximately the same time each day.*" It is acknowledged that the type of administration (i.e. oral gavage versus oral via diet) will impact the internal exposure profile, being a bolus administration in case of oral gavage, and by that it might affect the toxicological response. On the other hand, administration of the test item via oral gavage will result in a constant and more precise exposure during the gestation (unaffected by fluctuations in food consumption) when compared to applying exposure via the diet.
Further, most of the prenatal developmental toxicity studies with bentazone using oral gavage applied an exposure period during GD6-15. It is acknowledged that this does not comply with current OECD TG 414 which states that the test item should be administered daily from implantation to the day prior to scheduled caesarean section. This is a limitation. However, it is not expected that the observed adverse effects, i.e. post implantation loss, will disappear when the exposure period would be extended to the day prior to scheduled caesarean section.
Importantly, classification is based on the *intrinsic* hazards of a chemical, and classification does not take into account the exposure.
Overall, the Dossier Submitter considers there not to be valid reasons to disregard the prenatal developmental toxicity studies using oral gavage as administration route.
See further our response to subcomment 5b below.

2) In the summary of study Anonymous 1978 (Doc No 78/039) on page 35 of the CLH report it is referred to previous study (Anonymous 1971, Doc No 71/0041) by stating that "*The embryo-/fetotoxic effects as observed in Anonymous 1971 (Doc. No. 71/0041) were not reproducible when the study was repeated six years later on the same species and strain and using the same dosages of the test substance (Anonymous 1978, Doc. No. 78/039)*". In our opinion this is sufficiently and clearly described. Moreover, the CLH-report can not be adjusted during this phase of the CLH-process.

The studies with Klimisch score 3 or 4 are unacceptable for classification purposes and these studies are only considered as supplementary. This is already clearly mentioned in the overview table (Table 16), the study summaries (10.10.4) and in the discussion of the results of these studies (10.10.7).
Therefore we do not see that the conclusion that the study of El-Mahdi and Lofti (1988) provides supplementary information about time-dependence of fetal effects is misleading.

3) The information on vitamin K and warfarin are not included in the CLH-dossier for read-across purposes. We acknowledge that there are structural differences between the substance and warfarin which may affect toxicity and potency. The chapter on "Mechanism of action" is provided to indicate that inhibition of blood coagulation in developmental studies can be excluded as relevant mode of action for the increased post-implantation loss seen in developmental studies with Bentazone (i.e. to further substantiate that the increased post implantation loss can be considered a direct effect). An increased post-implantation loss was observed in the range 150-250 mg/kg bw/day. Whereas inhibition of blood coagulation can be expected in female animals at doses of >250 mg/kg bw/day. Changed hematological and clinicochemical parameters and shortened prothrombine time was seen in female rats at >250 mg/kg bw/day in various oral repeated dose studies (Doc. No. 87/0173, Doc No. 2011/1173365 and Doc No. 2012/1009658).

4a) Chapter 10.10.7, Table 32 gives a summary of the effects on post-implantation loss in the rat developmental studies. We agree that the Klimisch score should have been added to Table 32.

Study	**Strain and number of animals**	**Exposure period (gestation days)**	**Route**	**dose (mg/kg bw/day)**	**Post implantation loss**	**Maternal toxicity**
Anonymous 1991; Agrichem file no. R463	Wistar rat (n=5)	6-15	Oral, via gavage	450	Increased	No effect
				150	Increased	No effect
				50	Not increased	No effect
Anonymous 1991; Doc. No. Agrichem file no. R22 Klimisch score: 1	Wistar rat (n=25)	6-15	Oral, via gavage	360	Not increased	No effect
Anonymous 1986; Doc. No. 86/421 Klimische score 1	Wistar rat (n=25)	6-15	Oral, via gavage	250	Increased	No effect
				100	Not increased	No effect
				40	Not increased	No effect
Anonymous 1982; Doc. No. 84/066 Klimisch score: 3	Rat of the SD/CRJ strain (n=21-23)	0-21	Oral, via diet	631 (8,000 ppm)	Not increased	Reduced bw gain, hematuria, amniotic fluid and water consumption increased
				324 (4,000 ppm)	Not increased	No effect
				162 (2,000 ppm)	Not increased	No effect
Anonymous 1971; Doc. No. 71/0041	Sprague-Dawley rat (n=20-32)	6-15	Oral, via gavage	200	Increased	No effect

Klimische score 4						
				66.7	Not increased	No effect
				22.2	Not increased	No effect
Anonymous 1978; Doc. No. 78/039 Klimische score: 3	Sprague-Dawley rat (n=26-29)	6-15	Oral, via gavage	200	Not increased	No effect
				66.7	Not increased	No effect
				22.2	Not increased	No effect
El-Mahdi MM and Lofti MM 1988 Klimische score: 4	Rat (strain not specified)	Single dose on day 6, 8, 11,14, 16	Oral, via gavage	12.0	Increased	No details given
				43.2	Increased	No details given
				96	Increased	No details given

4b) Thank you for the suggestion. As stated above, the CLH-report can not be adjusted during this phase of the CLH-process. We agree that 7 losses were due to a total post-implantation loss in one female as is also mentioned the sentence "increased implantation loss was seen in one high dose rabbit". We agree that adding the number would be informative.

5a) Thank you for notice. The 205 should indeed be 250 mg/kg bw/day.

5b) We agree that the developmental studies did not include haematological or clinical biochemistry observations, which according to the repeated dose toxicity studies are more sensitive parameters affected by bentazone. The repeated dose toxicity studies are included in the discussion to indicate the type of maternal toxicity which can be expected at certain doses, being adverse effects on parameters which are not included in the developmental studies. We agree that in Doc ID 2011/1262233 an increasing dose by gavage yielded over proportional internal doses when a threshold dose (saturation of excretion of the substance or its metabolites) is reached. In this study the saturation of excretion started between actual dose levels of 84.7 and 165.9 mg/kg bw administered by gavage. However, it is unclear how this is related to the oral exposure via diet in repeated dose studies. There may be a difference in substance uptake and plasma concentrations after administration by gavage or via diet. This could indicate that in the developmental studies, where the route of administration is by gavage, there might be effects in maternal animals at dose levels where no effects were observed in the repeated dose studies using exposure via the diet. This indicates that there might be maternal toxicity at the dose range where implantation loss was seen. However, the results of developmental study (Doc. No. 84/066) with dietary exposure up to levels inducing marked maternal toxicity did not induce post-implantation losses although the dose levels were twice as high as in the main gavage study (Doc. No. 86/421) where post-implantation losses were seen but no maternal toxicity.

As mentioned in the OECD test guideline 414 the preferred route of administration is by gavage, therefore the developmental studies conducted by gavage are relevant to consider for classification.

Importantly, classification is based on the *intrinsic* hazards of a chemical as stated above, and classification does not take into account the (expected) human exposure.
Overall, the Dossier Submitter considers there not to be valid reasons to disregard the prenatal developmental toxicity studies using oral gavage as administration route. See also our response to sub-comment 1b.
The developmental toxicity studies revealed an effect on post implantation loss (resulting in a decrease in the number of live fetuses), primarily observed in the rat studies using oral gavage as administration type. The inconsistency in the results provides some uncertainty, making this a borderline case between category 1B and 2, and the Dossier Submitter proposes category 2.

RAC's response

Thank you for your comments and responses.

1) RAC agrees that the study with Klimisch score 3 should be considered acceptable and relevant for classification purposes.
2) RAC was not able to assess the reliability of study Doc ID 78/029 as the study report was in German. Some limitations were noted in the CLH dossier leading to some uncertainties on the results (mainly related to dosing). RAC agrees that the study El-Mahdi and Lofti is of poor quality (very low number of animals, unknown formulation)
3) RAC supports the dossier submitter's (DS's) response.
4) The reliability and limitations of the developmental toxicity studies have been addressed in the RAC opinion.
5) RAC agrees with the DS that studies performed by gavage could be considered for classification purposes and that the classification is based on the intrinsic hazards of the chemical.

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2020	Germany		MemberState	4

Comment received

The proposal to classify Bentazone as reproductive toxic substance is supported. As already described in detail by the DS, classification is indeed borderline between Repr. Category 2 and Category 1B.

The quality and reliability of the various rat studies is quite different and the Klimisch factors varies from 1 to 4. In the CLP Regulation, it reads, "If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification." Thus, the studies with a Klimisch factor of 3 or 4 should have a limited relevance to support a 1B-classification and a closer look on those studies with a convincing quality (Klimisch 1 and 2) appears appropriate to check the appropriateness of a 1B-classification.
The Klimisch 1-study from Anonymous (1986, Doc. No. 86/421) detected at the highest dose (250 mg/kg) an increased post-implantation loss (14.4 %) accompanied by a decreased fetal weight (-10.4 %) without significant maternal toxicity. The more recent Klimisch 1-study from Anonymous (1991, Agrichem file no. R 22) did not reproduce this finding though the design was comparable and the highest tested dose was even higher (360 mg/kg). Only a slightly reduced body weight of female fetuses (-4.3 %) without relevant maternal toxicity was observed. However, in both studies higher doses should have been applied, because relevant maternal toxicity was not detected in the highest doses, which were considered as maternal NOAELs. It should furthermore be noted, that the 2-generation-study in rats did not detect a postimplantion loss up to the highest dose

of 246.7 mg/kg, which was calculated for females after pairing (day 1 to day 21/22)). Due to the fact, that the post-implantation loss below maternal toxicity was not consistently observed in the available developmental toxicity studies in rats, the DS proposed classification in Category 2, which might be considered sufficient. However, it should be emphasised, that the available studies should at most considered as supplementary, as they do not comply with current test guidelines for developmental toxicity, in particular with regard to the shorter duration of treatment. With regard to the Two-generation reproductive toxicity study, a more detailed presentation of data would be helpful to follow the reasoning of the DS, that the reduced food consumption at 800 ppm should be considered as severe toxic. It is quite unusual to present only selected animal data to show reduced feed intake (which was not significant for the whole dose group). Based on the data shown, it cannot be excluded that the effect at mid dose level on day 1 to day 4 postpartum was transient and related to palatability. It would be appreciated to present maternal body weight/gain and feed intake in a tabulated form for all dose levels.
Dossier Submitter's Response

Thank you for your support for classification as reprotoxic. The Dossier Submitter proposed classification in Category 2 due to the fact, that the post-implantation loss below dose levels that induced maternal toxicity was not consistently observed in the available developmental toxicity studies in rats. It is noted that the dose levels in both developmental studies with klimisch score 1, Agrichem file no. R 22 and Doc. No. 86/421, were too low to detect relevant maternal toxicity. The higest doses were considered as maternal NOAELs. It is also noted that in 2001 the OECD test guideline 414 is revised and the duration of treatment was extended to include the third trimester of gestation. Both studies were performed before this revision and therefore do not comply with the current OECD test guideline 414. This is a limitation. However, it is not expected that the observed adverse effects. i.e. postimplantation loss, will disappear when the exposure period would be extended to the day prior to scheduled caesarean section.

In the two-generation study (Doc. No. 89/0068) the observed reduced pup weight at PND4 and 7 at 800 and 3200 ppm is unlikely to be directly caused by the substance or the substance via lactation, but rather a consequence of maternal toxicity (manifested as reduced feed intake during PND1-4). Please find the individual maternal body weight gain and feed intake of all dams in mid-dose and high-dose groups in the tables below. In the RAR of Bentazone the average intake of D0-7, D7-14 and D14-21 are added together. In this table the Dossier Submitter presented the average intake of each dam per period during gestation. The Dossier Submitter also added information regarding mean pup weight gain during D1-4 and D4-7. At 800 ppm dams # 159 and #164 lost their entire litters by day 4 post partum. At 3200 ppm dam # 191 lost its entire litter by day 4 post partum. This finding in litter loss was considered not to be related to treatment with the test substance. At 3200 ppm for dam # 196, 15 pups were found dead on day 0 p.p., partly cannibalized.

Taking only those dams of the 800 ppm group into account which had a total litter loss or whose pups showed reduced pup weights over the period of PND 1-4 which are #152, 155, 156, 159, 164, 167, 171, 172 and 175, the mean maternal food consumption between PND 1 and 4 is 14.2 ± 9.6 g (see Table 19A). This is a significant reduction of about 52% compared to the control and the body weight gain was reduced to 4.8 g between PND 1 and 4, which is only 29% of the concurrent control.
A further focusing on only those dams that showed a body weight reduction based on maternal toxicity and not those that had reduced pup weight based on high litter size would additionally eliminate dam #152 and #172. This leads to a reduced food consumption of 10.4 ± 6.7 g (38.3% of control) and the mean maternal body weight gain to -1.7 g between PND1 and 4. This clearly demonstrates a pronounced maternal toxicity at 800 ppm based on a significantly reduced food intake and weight gain values.

Table 19A: P-generation nursing the F1 pups: 800 ppm groups; Individual maternal food consumption data and body weight respective Body weight gain of the F0 dams and the corresponding F1 litter body weight means and litter size.

800 ppm Dam #	Food consumption [g/animal/day]												BW [g]	BWG [g]	Mean Pup weight [g]			
	Gestation*						Lactation						maternal					
	Days 0-7	Dev. to Control (%)	Days 7-14	Dev. to Control (%)	Days 14-21	Dev.to Control (%)	Days 1-4	Dev.to Control (%)	Days 4-7	Dev.to Control (%)	Days 7-14	Dev.to Control (%)	PND 1	PND 1-4	Litter size	PND1	Days 1-4	Days 4-7
151*																		
152	**21**	**107**	**20**	**100**	**19**	**94**	**25**	**92**	**41**	**105**	**47**	**92**	**218**	**33**	**14**	**5.1**	**1.5**	**4.6**
153	18	92	19	95	20	99	24	88	35	89	47	92	237	8	11	5.2	2.5	4.4
154	23	117	22	110	23	114	24	88	37	94	47	92	254	16	12	5.9	1.9	4.4
155	**19**	**97**	**21**	**105**	**20**	**99**	**5**	**18**	**33**	**84**	**49**	**96**	**244**	**-9**	**13**	**5.4**	**-0.6**	**3.1**
156	**22**	**112**	**22**	**110**	**23**	**114**	**19**	**70**	**35**	**89**	**47**	**92**	**253**	**7**	**15**	**4.9**	**1.4**	**4.7**
157	20	102	19	95	19	94	21	77	36	92	48	94	221	12	11	5.3	2.5	4.7
158	21	107	20	100	18	89	11	40	30	77	41	81	233	-6	5	5.4	3.7	5
159	**24**	**122**	**22**	**110**	**24**	**119**	**3**	**11**	**-**	**-**	**-**	**-**	**258**	**-5**	**14**	**5.7**	**-**	**-**
160	22	112	22	110	22	109	41	151	37	94	61	120	222	34	13	6.0	2.7	5.9
161	27	138	28	140	28	138	32	118	37	94	56	110	299	2	11	6.3	3.5	5.8
162	20	102	19	95	20	99	48	177	39	99	50	98	245	24	11	5.8	3	5.4
163	20	102	21	105	22	109	26	96	37	94	50	98	259	22	10	5.7	2.8	4.4
164	**22**	**112**	**22**	**110**	**23**	**114**	**10**	**37**	**-**	**-**	**-**	**-**	**279**	**-26**	**5**	**5.5**	**-**	**-**
165	20	102	21	105	21	104	32	118	42	107	54	106	258	27	10	6.5	3.2	5.8
166	20	102	20	100	20	99	27	99	39	99	52	102	249	31	14	5.1	2.2	4.4
167	**21**	**107**	**20**	**100**	**21**	**104**	**14**	**51**	**32**	**82**	**37**	**73**	**263**	**4**	**9**	**5.8**	**-0.3**	**3.6**
168	19	97	18	90	18	89	21	77	36	92	52	102	235	16	12	5.5	2.5	5.7
169	20	102	20	100	20	99	35	129	44	112	57	112	232	33	15	5.2	3	5.9
170	19	97	21	105	22	109	41	151	42	107	61	120	253	38	13	4.9	2.4	4.9
171	**23**	**117**	**23**	**115**	**19**	**94**	**4**	**15**	**28**	**71**	**52**	**102**	**261**	**-14**	**13**	**5.2**	**0.4**	**3.6**
172	**20**	**102**	**22**	**110**	**-**	**-**	**30**	**110**	**42**	**107**	**55**	**108**	**259**	**22**	**15**	**4.9**	**1.9**	**5.4**
173	21	107	21	105	21	104	24	88	35	89	49	96	233	10	12	5.7	1.6	4.9
174	21	107	20	100	21	104	36	132	32	82	47	92	240	35	12	5.6	1.9	4.8
175	**17**	**87**	**19**	**95**	**19**	**94**	**18**	**66**	**62**	**158**	**47**	**92**	**224**	**31**	**11**	**5.0**	**1**	**4.3**
Mean	20.8	106.2	20.9	104.4	21.0	103.9	**23.8**	**87.5**	37.8	96.4	50.3	98.8	**247**	**14**		**5.5**	**2.0**	**4.8**
												Dev. to control	**100**	**86**		**92**	**79**	**95**
Taking only those dams which had a total litter loss or whose pups showed reduced pup weights over the period of PND 4-7 which are #152, 155, 156, 159, 164, 167, 171, 172 and 175																		
Mean	21.0	107.0	21.2	106.1	21.0	104.0	**14.2**	**52.3**	39.0	99.4	47.7	93.6	**251**	**4.8**		**5.3**	**0.8**	**4.2**
												Dev. to control (%)	**102**	**29**		**88**	**29**	**83**
Under exclusion of #152 and # 172 which showed reduced pup weight despite normal food intake																		

Mean	21.1	107.7	21.3	106.4	21.3	105.4	**10.4**	**38.3**	38.0	96.8	46.4	91.0	**255**	**-1.7**		**5.4**	**0.4**	**3.9**
												Dev. to control (%)	**103**	**-10.3**		**90**	**15**	**76**

* female was not pregnant

In addition to the analysis of the 800 ppm group as presented in the RAR of bentazone, the Dossier Submitter conducted a similar analysis for the 3200 ppm group as well which is presented below (see Table 19B). Taking only those dams of the 3200 ppm group into account which had a total litter loss or whose pups showed reduced pup weights over the period of PND 1-4 which are #182, #185, # 189, #191, and #194, the mean food consumption during lactation period was reduced compared to the control (Table 19B). Between PND 1 and 4 the food consumption was reduced about 63% compared to the control. In contrast to the dams in the 800 ppm group the body weight gain was not reduced between PND 1 and 4 compared to the control.

A further focusing on only those dams that showed a body weight reduction based on maternal toxicity and not those that had reduced pup weight based on high litter size would additionally eliminate dam # 182. This leads to a reduced food consumption of 50.3% of control and the mean maternal body weight gain to 13.5 g between PND1 and 4 (80.9% of control). This demonstrates an more pronounced maternal toxicity at 3200 ppm based on a significantly reduced food intake.

Overall pup weight effects are correlated to higher litter size and/or to significant reduced maternal feed intake within the early lactation phase. Therefore the pup weights effect are not likely to be substance related.

Table 19B: P-generation nursing the F1 pups: 3200 ppm groups; Individual maternal food consumption data and body weight respective Body weight gain of the F0 dams and the corresponding F1 litter body weight means and litter size.

3200 ppm Dam #	Food consumption [g/animal/day]												BW [g]	BWG [g]	Mean Pup weight [g]			
	Gestation*						Lactation						maternal					
	Days 0-7	Dev. to Control (%)	Days 7-14	Dev. To Control (%)	Days 14-21	Dev.to Control (%)	Days 1-4	Dev.to Control (%)	Days 4-7	Dev.to Control (%)	Days 7-14	Dev.to Control (%)	PND 1	PND 1-4	Litter size	PND1	Days 1-4	Days 4-7
176	18	92	18	90	21	104	31	114	39	99	50	98	214	28	12	5.7	2.4	4.6
177	23	117	24	120	27	134	40	147	40	102	53	104	273	9	14	6.3	2.7	5.6
178	18	92	20	100	21	104	27	99	37	94	47	92	227	18	8	6.2	3	4.1
179	15	76	15	75	19	94	22	81	33	84	43	84	206	18	10	5.4	1.9	4.8
180	18	92	17	85	19	94	24	88	36	92	49	96	218	13	9	6.0	2.4	4.3
181	18	92	20	100	21	104	34	125	36	92	50	98	213	20	10	5.8	2.7	4.5

182	**21**	**107**	**22**	**110**	**22**	**109**	**31**	**114**	**40**	**102**	**52**	**102**	**248**	**35**	**15**	**4.8**	**1.4**	**4.6**
183	18	92	17	85	20	99		-	-	-	49	96	240	16	11	5.6	1.4	4.7
184	22	112	21	105	22	109	24	88	43	110	51	100	223	29	13	5.5	2.2	5.4
185	**19**	**97**	**18**	**90**	**11**	**54**	**20**	**74**	**30**	**77**	**40**	**79**	**219**	**18**	**6**	**5.0**	**1.6**	**3**
186	15	76	17	85	18	89	23	85	37	94	43	84	211	26	10	6.2	2.3	5.3
187	23	117	24	120	25	124	37	136	57	145	49	96	260	26	13	5.7	3	4.2
188	19	97	21	105	22	109	30	110	42	107	49	96	251	24	13	5.4	1.6	4.7
189	**18**	**92**	**18**	**90**	**20**	**99**	**14**	**51**	**36**	**92**	**47**	**92**	**199**	**13**	**13**	**4.6**	**0.3**	**3.5**
190	21	107	22	110	27	134	28	103	43	110	56	110	243	27	12	6.2	2.4	5.7
191	**16**	**82**	**17**	**85**	**18**	**89**	**1**	**4**	**-**	**-**	**-**	**-**	**181**	**-8**	**11**	**4.5**	**-**	**-**
192	19	97	19	95	21	104	21	77	36	92	45	88	225	8	10	5.4	2.4	4.5
193	20	102	20	100	22	109	26	96	37	94	49	96	242	13	11	5.6	2.9	5.1
194	**20**	**102**	**21**	**105**	**21**	**104**	**20**	**74**	**40**	**102**	**52**	**102**	**232**	**31**	**14**	**5.0**	**0.8**	**4.2**
195	21	107	21	105	24	119	30	110	44	112	58	114	223	31	11	5.6	2.5	5.4
196	20	102	18	90	17	84	-	-	-	-	-	-	185	-	-	-	-	-
197	19	97	19	95	20	99	25	92	35	89	50	98	231	25	11	5.1	2.6	5.4
198	15	76	19	95	19	94	26	96	38	97	46	90	212	21	11	5.4	2.6	4.3
199	20	102	20	100	20	99	28	103	41	105	56	110	234	27	12	5.4	2.3	4.7
200	21	107	22	110	23	114	29	107	39	99	49	96	218	23	10	6.8	2.5	4.7
Mean	19.1	97.3	19.6	97.8	20.8	102.9	**25.7**	**94.5**	39.0	99.6	49.3	96.80	**225.1**	**20.5**		**5.6**	**1.9**	**4.7**
Dev. to control													**91.1**	**122.6**		**93**	**73**	**92**
Taking only those dams which had a total litter loss or whose pups showed reduced pup weights over the period of PND 4-7 which are #182, #185, # 189, #191, and #194,																		
Mean	18.8	96.0	19.2	96.0	18.4	91.0	**17.2**	**63.0**	36.5	93.0	47.8	93.5	**215.8**	**17.8**		**4.8**	**1.0**	**3.8**
Dev. to control (%)													**87.3**	**106.7**		**80.0**	**39.7**	**75.5**
Under exclusion of #182 which showed reduced pup weight despite normal food intake																		
Mean	18.3	93.3	18.5	92.5	17.5	86.5	**13.8**	**50.3**	35.3	90.0	46.3	90.7	**207.8**	**13.5**		**4.8**	**0.9**	**3.6**
Dev. to control (%)													**84.1**	**80.9**		**79.9**	**34.9**	**70.4**

RAC's response

Thank you for your comment and response.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2020	Germany		MemberState	5
Comment received				
Classification as Acute Tox. 4 (H302: Harmful if swallowed) is supported.				
Dossier Submitter's Response				
Thank you for your support on classification with Acute Tox. 4 (H302).				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2020	France	BASF	Company-Manufacturer	6
Comment received				
The CLH report, chapter 10.7.2 p 16, mentions some doubts on the results of the open epicutaneous test (OET) performed with bentazone sodium (600 g/L) due to the lack of dose response. It is mentioned that a subcategorization is not possible with the current data as the study is not a Buehler test. The lack of sensitizing properties of the undiluted formulation bentazone sodium salt (600 g/L) as tested in the OET is confirmed by a valid Bühler assay with a comparable formulation containing 700 g/L bentazone sodium salt (BAS 351 56 H, Doc ID 2015/1004047). In this valid and negative Bühler assay the induction and challenge were conducted with the neat test item. No signs of sensitization were observed. In case this negative Bühler assay at > 20% topical induction dose is considered helpful for subcategorization in 1B, it can be submitted on request. A further testing in a maximization or a Bühler assay at a lower induction concentration than the highest to cause mild-to moderate skin irritation is considered not in accordance with the guideline OECD 406. Only the OET was designed from the beginning onwards as a multiconcentration test to account for dose-response properties. In view of this it seems worth mentioning that the OET assay was, in addition to the Bühler assay, part of OECD No. 406 (adopted 12 May 1981) as Non-Adjuvant test and both were indiscriminately considered as equal with respect to their evidence. The most obvious difference as tabularly presented in Schlede et al., 1989 (Arch Toxicol 63: 81-84) is the use of several open applied concentrations in the OET compared to the fixed concentrations applied occluded in the the Bühler assay. So, it is rather the higher number of animals (due to several concentrations) and the open application area than a lower reliability that deemed the OET as less applicable. Under a weight of evidence approach using all data including the OET as similar sensitive than the Bühler would support a subcategorization in Skin Sens 1B.				
Dossier Submitter's Response				
Thank you for sharing the results of a Bühler assay with a formulation containing 649.7 g/L bentazone sodium salt (BAS 351 56 H, Doc ID 2015/1004047). The Dossier Submitter has evaluated this study. Below, a summary of this study is provided. Further, a comparison with the CLP criteria is presented based on the overall data on skin sensitisation. <u>Summary study Doc ID 2015/1004047:</u>				

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
The study was performed according to OECD 406 (Maximization test) GLP: yes	20 female Pirbright White Guinea pigs	bentazone (purity: 94.0%; batch no. MS 2 F 22)	intradermally applied as aqueous solution [5% in aqua dest. or in Freund's adjuvant/aqua dest. (1:1)]	Sensitising to skin: 12/20, 6/20 and 16/20 animals tested positive at 1st, 2nd and 3rd challenge	Anonymous 1986 (Doc. No. 86/195)[a] Klimisch score: 1
The study was performed according to OECD 406 (OET). GLP: yes.	eight female Pirbright White guinea pigs	Bentazone sodium salt formulation (600 g/L; batch no. WH 4976)		Sensitizing at 50% aqueous dilution: 2/8 and 3/8 animals tested positive at 1st and 2nd challenge Not sensitizing at 2% and 10% aqueous dilution	Anonymous 1986 (Doc. No. 86/221)[a]
The study was performed according to OECD 406 (Bühler method) GLP: yes.	20 male Hartley albino guinea pigs	Bentazone (649.7 g/L; batch no. FRE-001033)	100 % of test substance was topically applied using an occlusive 25 mm Hill Top Chamber	Sensitization response: 0/20 and 0/20 animals tested positive at challenge after 24 and 48 hours	Doc ID 2015/1004047

The Bühler test used test groups consisting of 20 animals for the treated group and 10 animals for the controls. A historical positive control validation study was recently performed using alpha-Hexylcinnamaldehyde, ≥ 95% (HCA) as a positive control. Twenty eight days after the first induction dose at the highest non-irritating concentration (determined in the preliminary irritation screen to be 100% of the test substance) was applied to a naive site on each guinea pig. A naive control group (ten animals) was maintained under the same environmental conditions and treated with the test substance at challenge only. No skin reactions were noted in animals of the control and test groups 24 and 48 hours after challenge. Appropriate results were obtained in the historical positive control validation study with ≥ 95% HCA (8/10 positive response upon 24 and/or 48 hours after challenge).

The results after the challenges are compiled in the Table below.

	Sensitization Response Indices			
	Incidence of Positive Response[1]		Severity[2]	
	Hours		Hours	
	24	48	24	48
Test animals	0/20	0/20	0.00	0.00
Naïve Control Animals	0/10	0/10	0.00	0.00

[1] Animals with scores greater than 0.5
[2] Sum of the erythema scores divided by the number of animals evaluated.

Comparison with the CLP criteria:
No skin reactions were observed in a Bühler test after topical induction with 0.5 mL of the Bentazone (649.7 g/L = 65%) was applied (Doc ID 2015/1004047).

However, positive skin reaction in 12/20 animals after first challenge, 6/20 after second challenge and 16/20 after third challenge were observed in a maximization study after intradermal induction with 5% bentazone (purity: 94.0%) (Doc. No. 86/195).
In the open epicutaneous test (OET) concentration of 50% (of 600 g/L = 30%) in aqua dest. for induction and challenge showed a positive response in 2/8 (25%) after first challenge and 3/8 (38%) after second challenge (Doc. No. 86/221).

Overall, the maximization study and the OET indicate a skin sensitization potential. The positive response of the maximization study corresponds to a category 1B. Classification into sub-categories is required when data are sufficient (CLP Annex I 3.4.2.2.1.1). When Category 1A cannot be excluded, Category 1 should be applied instead of Category 1B. In this case only data are available from guinea pig tests showing a high response after exposure to a high concentration (GPMT test) but where lower concentrations which could show the presence of such effects at lower doses are absent. Unless there is sufficient evidence to place such substances in sub category 1A or 1B, classification in category 1 should be the default.
It is noticed that the data are inconsistent with a clear positive response in the GPMT (and OET) and a negative response in the Bühler assay. There is no clear explanation for this inconsistency and according to the Dossier Submitter all data should be taken forward for classification.
Overall, the available data indicate a requirement for classification. However, these data are not conlusive for sub-categorisation and in that case skin sensitisers shall be classified in category 1.

Conclusion on classification and labelling for skin sensitisation:
Bentazone should be classified as Skin Sens. 1 (H317 May cause an allergic skin reaction).

RAC's response
Thank you for your comment and answer, RAC agrees with the DS assessment of the study.

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2020	Germany		MemberState	7
Comment received				
Based on the available data presented classification without sub-categorisation as Skin Sens. 1 (H317 May cause an allergic skin reaction) is supported.				
Dossier Submitter's Response				
Thank you for your support on classification with Skin Sens. 1 (H317).				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2020	Germany		MemberState	8

Comment received

The German CA agrees that no acute classification for the aquatic environment is necessary for bentazone. The DS proposal that no chronic classification for the aquatic environment is necessary (removal of current Annex VI entry: Aquatic Chronic 3, H412) for bentazone is not supported.

The available chronic data for bentazone - especially for algae and aquatic plants - are sufficient for the classification with Aquatic Chronic 2, H411, especially EC10/NOEC values ≤ 1 mg/L are available (Ref. Dohmen, 1990 using the green alga Ankistrodesmus bibraianus (current name Selenastrum bibraianum Reinsch). Additionally, reliable data of bentazone for toxicity to embryo of Xenopus laevis are available, with lowest NOEC of 0.015 mg/L and hints to be teratogenic for frogs at this study.

Bentazone is a surface-active substance with a surface tension of 45.6 mN/m (at a concentration of 1.02 g/L) and with a CT50 of > 10 d from the bioconcentration study with fish Lepomis macrochirus. Therefore, log Kow of -0.46 (buffered at pH 7) and the bioconcentration factor of 1.4 L/kg are not sufficient for the classification and labelling purpose.

Dossier Submitter's Response

Thank you for your response. Your questions and remarks are addressed below.

It is unclear to the Dossier Submitter how the German CA reached the conclusion that Aquatic Chronic 2, H411 is warranted.

- The two Dohmen studies were considered unacceptable by the RMS in the RAR, as the test item concentrations were not analytically verified and because the followed test guideline was outdated. The Dossier submitter only had access to the summary as presented in the RAR, and which was included 'as is' in Annex I to the CLH report. The available data did not allow to reassess if validity criteria were met (e.g. exponential growth of the control), nor could the Dossier Submitter determine to what extent the followed test guideline deviated from the current OECD 201 test guideline. Therefore, the we can only rely on the previous assessment, and conclude that the study is unreliable. Alternatively, the study would be considered unassignable, and the data would also not be used for classification purposes. That said, neither of the algal growth inhibition studies reported a chronic effect concentration below 1 mg/L, i.e. Dohmen (1990a; STUDY IIA, 8.4/03) reported an 72h-E_bC10 of ~1.5 mg/L (expressed as nominal), and Dohmen (1990b; STUDY IIA, 8.4/04) an 72h-E_bC10 of 5.0 mg/L (expressed as nominal). Please do note that these two chronic effect concentrations were omitted by mistake from the report, and have only been reported in Annex I to the CLH report.
- Regarding the Xenopus study, Annex I to the CLH report contains a summary of a literature study (Orton et al., 2009; https://doi.org/10.1021/es8028928) that used cultured *Xenopus* oocytes to measure effects of bentazone (conc. 0.000625 – 62.5 µM) on the ovulatory response and ovarian steroidogenesis. No effect were observed in this study.

Table 8 of the CLH report reports surface tensions of 68.9, 69.2 and 70.0 mN/m for bentazone in 0.5%, 2.0% and 0.421 g/L test solutions. As these surface tension values

are all above 60 mN/m, bentazone is not considered a surface active substance. The value of 45.6 mN/m (at a concentration of 1.02 g/L) reported by the German CA cannot be verified. That said, even if bentazone was considered surface active this would not affect the classification proposal as bentazone is considered not rapidly biodegradable.
RAC's response
RAC agrees with the DS's response.

Date	Country	Organisation	Type of Organisation	Comment number
19.12.2019	Sweden		MemberState	9
Comment received				
The Swedish CA agrees with the proposal to remove the environmental classification; Aquatic chronic 3, H412. Based on the lowest growth rates for lemna; acute EC50 and chronic ErC10 of 12 mg/L and 3.2 mg/L, respectively, there is no need for neither acute nor chronic environmental hazard classification.				
Dossier Submitter's Response				
Thank you for your response and support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
10.01.2020	France		MemberState	10
Comment received				
FR: We agree with the proposition for bentazone to be not classified and with the justification of not using the value of the metabolite N-methylbentazone 28 d NOEC = 0.23 mg/L for Oncorhynchus mykiss for the proposal.				
Dossier Submitter's Response				
Thank you for your response and support.				
RAC's response				
RAC agrees with the DS and the commenting MSCA regarding the use of metabolite N-methylbentazone.				

Date	Country	Organisation	Type of Organisation	Comment number
10.01.2020	United Kingdom		MemberState	11
Comment received				
Chronic toxicity to fish endpoint: The CLH report includes a 35d NOEC of 9 mg/L from an OECD 210 limit test. This endpoint is based on survival and body weight. It is noted that there was a significant difference in mean body length between the control and limit treatment. As this was based on an increase in body length in treatment fish, the CLH report considers this endpoint is not relevant for NOEC determination. We consider further information is required to support this position. For example, what were the measurements to understand how much of an increase was observed and at what statistical probability? In addition, why would an increase not be considered relevant and was the increase seen across all 4 treatment replicates or was it driven by potential				

outlier measurements? It would be useful to present this information and the raw length data to consider if the study endpoint is reliable. However, we note that such evaluation of this endpoint will not impact the classification.

Algal / aquatic plants endpoint:
The CLH report notes that the Munkegaard et al. (2008) study with Lemna minor and Pseudokirchneriella subcapitata is considered Klimisch 4 (unassignable) and the data are not considered further in relation to hazard classification. Based on the available data we support this position.

We note that bentazone is a herbicide although the tested algal and Lemna species do not appear to be sensitive. In contrast, non-target terrestrial plants are highly sensitive (RAR, 2014). This difference in sensitivity may be due to the selective mode of action of bentazone which is targeted towards broadleaved weeds. Other aquatic plant species may be more sensitive than the Lemna and algal species included in the CLH report. It may therefore be necessary to revise the classification if data on other plant species become available in the future.

Degradation product N-methyl-bentazone.
The CLP report highlights that the water-sediment degradation product N-methyl-bentazone is more toxic to fish and aquatic invertebrates than bentazone, as presented in the EFSA conclusion and RAR. The CLP report notes that "considering that degradation of bentazone in water is a slow process, that the formation of N-methyl-bentazone is reversible, and that the presence of N-methyl-bentazone will result in a more conservative assessment of bentazone toxicity, the classification will be conducted based on studies conducted with bentazone".

There was a maximum formation of 13% N-methyl-bentazone in the three water-sediment degradation studies presented in the CLH report. This compound was almost exclusively in the water phase.

On this basis, we do not think that the level of N-methyl-bentazone produced within the timeframe of acute toxicity studies is a concern and therefore data do not impact the acute hazard classification.

Although degradant formation is slow and reversible, we think that it is relevant to consider this degradation product when evaluating the chronic hazard classification of the parent compound bentazone to the aquatic environment. As a worst-case, we can estimate the contribution of N-methyl-bentazone to the overall long-term aquatic toxicity of bentazone at this maximum level of 13% using the lowest chronic endpoint for N-methyl-bentazone as shown below:

$0.23 \times (100/13) = 1.77$ mg/L.
(Lowest reliable NOEC for N-methyl-bentazone × (100 / maximum % AR of N-methyl-bentazone in degradation studies)

This estimate produces a NOEC above 1 mg/L, indicating that no aquatic chronic classification for bentazone is required when the degradation product is taken into account. We note that the RAR has conducted a risk assessment on N-methyl-bentazone and similarly identified a low risk to the aquatic environment.

Overall, we feel the CLH proposal / opinion should consider the relevance of degradant

data and provide explanation as to how the toxicity of N-methyl-bentazone is considered in the classification of bentazone.

Dossier Submitter's Response

Thank you for your response. Your questions and remarks are addressed below.

Regarding chronic fish toxicity, we agree that a significant increase in fish body length should not be discarded a priory as not being adverse. That said, we only have access to the summary as presented in the RAR, and which we included 'as is' in Annex I to the CLH report. Unfortunately, the summary did not report the mean length increase of the treated fish, the number of fish that were affected, the raw data for fish length (or any other endpoint), nor the statistical methodology used. We are thus not in a position to re-evaluate the study. In the CLH report we noted that "*The registrant concluded that as an increase is considered not an adverse effect, this effect was not taken into account for determination of the NOEC*", and "*Study was considered acceptable in the RAR*". We should have made it clearer that we based our assessment on the conclusion of the RMS who had access to the study report, and who considered the results as reliable without restrictions. Their assessment would have been discussed with other member states and EFSA during the renewal procedure, and we assume that if the increase in body length was detrimental this would have been noted. We therefore decided against discarding this study as being unassignable. It should be noted that in the latter case, there would be a data gap for chronic fish toxicity, as the fish, juvenile growth test with the formulated product was considered unreliable in the RAR. Using the surrogate approach (bentazone is not rapidly degradable) and the fact that the lowest acute effect concentration was a 96h-LC50 of >94 mg/L for the fish *Lepomis macrochirus*, this would also result in no chronic classification.

Regarding algal/aquatic plants endpoint, we agree that if new data for more sensitive primaire producers becomes available, the classification should be revised to reflect these new findings.

Regarding the degradation product N-methyl-bentazone, the CLH report already notes that during testing of the parent substance, N-methyl-bentazone is formed. As the latter substance is more toxic, the effects observed in the studies can at least partly be attributed to N-methyl-bentazone. As such the toxicity of the degradation product is indirectly taken along in the classification proposal. In our opinion, this is enough and there is no need to further discuss the studies conducted with N-methyl-bentazone alone. We do acknowledge that your calculation based on the lowest NOEC for N-methyl-bentazone and the maximal formation in a water/sediment system of 13% is supportive for not classifying bentazone for chronic aquatic toxicity.

RAC's response

Chronic toxicity to fish endpoint:
RAC recognises the DS's explanation on not having access to the original study report and the fact that the study has been evaluated in the pesticide assessment process. Because there were no effects in the acute study giving the lowest LC_{50} value for fish, the surrogate approach would also lead to no classification for chronic effects.
Algal / aquatic plants endpoint:
RAC agrees with the commenting MSCA and the DS. A sentence concerning revision of classification in case of new data is added to the opinion.
Degradation product N-methyl-bentazone:
RAC agrees with the DS's view.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BENTAZONE (ISO); 3-ISOPROPYL-2,1,3-BENZOTHIADIAZINE-4-ONE-2,2-DIOXIDE

Date	Country	Organisation	Type of Organisation	Comment number
10.01.2020	Belgium		MemberState	12

Comment received

The Belgian CA supports the conclusion that no classification of Bentazone is warranted for environmental hazards:
Acute aquatic toxicity: all L(E)C50 > 1mg/L : no classification
Chronic aquatic toxicity: most sensitive species is algae (Lemna gibba) with 7dErC10=3.2 mg/L > 1 mg/L and Bentazone is not rapidly degradable

Although not affecting the classification outcome, we are of the opinion that also the surrogate approach should be considered for chronic toxicity as for invertebrates only studies are available with a formulation containing +/- 40% of Bentazone and thus not with the substance as such.
Reliable chronic data are available for fish and algae. For the other trophic level (invertebrates), the 48hEC50 >100 mg/L and the substance is not rapidly degradable, resulting in no classification for environmental hazards.

Some editorial comments :
P.66 first paragraph: Acute fish (Cypridon variegatus), anonymous (1991): 137.5-146.2.9%
P.72 table 18 OECD TG 215 (Oncorhynchus mykiss), Document III/section 10.2.5/01: 21d-NOEC should read 28d-NOEC
p.73 table 18: Basagram was tested by Jatzek, 1989a and Bentazone 480g/L SL by Migchielen, 2001 instead of the inverse.

Dossier Submitter's Response

Thank you for your response and support, as well as pointing out the editorials.

We agree that aquatic toxicity studies performed with the active substance are preferred above studies conducted with the formulated product, as in the latter case it can never be fully excluded that other substances present in the formulation might have affected the outcome of the test. By expressing the effect concentrations based on the active substance (as we did), we attributed all toxicity to the active substance. This reasonable worst-case approach does not warrant a chronic aquatic classification. While in our opinion the surrogate approach is not deemed necessary, i.e. there are realiable chronic data for aquatic invertebatres, we do acknowledge that it is supportive for not classifying bentazone for chronic aquatic toxicity.

RAC's response

RAC is of the opinion that formulation studies can be used for classification only when there is detailed information on the other substances present in the formulation. Co-formulants serve different purposes in the products and might have an effect to the overall toxicity of a product. Therefore, RAC is of the opinion that the classification should be based on the surrogate approach.