Committee for Risk Assessment

RAC

Annex 2
Response to comments document (RCOM)
to the Opinion proposing harmonised classification and labelling at EU level of

Dicamba

EC Number: 217-635-6
CAS Number: 1918-00-9

CLH-O-0000007132-84-01/F

Adopted

2 June 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DICAMBA (ISO); 2,5-DICHLORO-6- METHOXYBENZOIC ACID; 3,6- DICHLORO-2-METHOXYBENZOIC ACID

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: dicamba (ISO); 2,5-dichloro-6- methoxybenzoic acid; 3,6-dichloro-2-methoxybenzoic acid
EC number: 217-635-6
CAS number: 1918-00-9
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2021	Germany		MemberState	1
Comment received				
DE CA supports the proposed classification and labelling as presented in the CLH report and above, i.e. Acute Tox. 4, H302, Acute Tox. 4, H332, Eye Dam. 1, H318, Carc. 2, H351, STOT SE 3, H335, STOT SE 3, H336. However, we have a formal comment on the dossier. In section 2.11.2.1, table 117 the ATE value have to be add with (dusts or mists) and the value must be given as 4,46 mg/L.				
Dossier Submitter's Response				
Agree with comment (dusts or mists) should have been added.				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	2
Comment received				
The comments for several points are extensive and complex. Please note that all complete comments are attached as pdf file to this submission. Please consider the complete comments from the attached pdf. Additional information are also submitted as attached pdfs. Details to this additional information are pointed out in the detailed comments.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip
Dossier Submitter's Response
Noted
RAC's response
Thank you very much for your comment. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	3
Comment received				
FR: • 1.3.7 (p12): Specification of purity of the active substance in g/kg is not confidential. Please, add it. • (p59): For more clarity, please add the active substance purity used in the determination of vapour pressure and surface tension. • (p59): For more traceability, please add in the table the methods used for the determination of physico-chemical properties.				
Dossier Submitter's Response				
Agree that minimum purity of the active substance is not confidential. The purity should be stated. The purity of the active substance used for determination of vapour pressure and surface tension could be added. The methods used for the determination of physical and chemical properties could be added in the table.				
RAC's response				
Thank you very much for your comment. Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	4
Comment received				
• Vol. 1, 2.6.5, Carcinogenicity: Rotam is of the opinion, that dicamba should not be classified as Carc Cat 2 substance, since thyroid parafollicular (C-cell) carcinoma found at 250 ppm and above should be considered age and not substance related. Incidence of thyroid C-cell carcinomas in male rats only slightly exceeded the range of HCD. In general, in older animals, spontaneously formed tumours increase with every additional week. In case of the reported study HCD do not cover the most critical time (2.5 and 3.5 month longer than HCD for males and females, respectively). Based on WoE (missing increase in thyroid C-cell (pre-) neoplastic lesions and occurrence of tumours not earlier than in control animals) a relationship to treatment is considered unlikely. • Vol.1, 3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS: The slightly higher incidences of amyloidosis found in the study should not be				

used to support the classification for Carc Cat 2. Amyloidosis are generally not considered as neoplastic lesions. The slightly higher incidences are considered to be within the normal biological range of aging mice and the occurrence of amyloidosis was not associated with an increased incidence of neoplastic findings in the respective organs. Hence, the findings are not suitable to support classification for Carc. Cat 2.

• If evaluators agree with the proposals above, "Cat. 2 H351" should be deleted based on the fact that thyroid carcinomas are quite common in aging rats and amyloidosis are not considered as neoplastic lesions and the observed incidences were within range of HCD.

Dossier Submitter's Response

• Vol. 1, 2.6.5, Carcinogenicity:
HCD can be a relevant factor in evaluating the treatment-relationship. Agree that the available HCDs were not ideal and that age, among other confounding factors, may affect the incidence of various types of cancer. However, dose-response (positive trend test) was observed in the incidence of thyroid parafollicular c-cell carcinoma.

• Vol.1, 3.1.9: In humans amyloidosis may in some people be associated with some forms of cancer (multiple myeloma and non-Hodgkin's lymphoma). We are not aware that a link between amyloidosis and carcinogenesis has been esthablished other than, as mentioned, amyloidosis is sometimes seen in people with multiple myeloma or non-Hodgkin's lymphoma.

RAC's response

Thank you very much for your comment. RAC concurs with the DS that the HCD databases are not ideal. RAC has assessed the reliability of the provided HCD and considered only 2 of them to be valid; specifically, those obtained by the same performing laboratory and within a temporal frame of ±5 years. RAC also concurs with the DS that amyloidosis is not a relevant effect for assessing carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	5

Comment received

Syngenta: Considers a Carc Cat 2 classification as not required for dicamba .
1. Reference: Vol.1 – level 2, 2.6.5, pages 132, 137-141: incidence of thyroid C-cell carcinomas and uterus polyps in combined carcinogenicity/chronic toxicity study in rats (in-life period 26.5 and 27 months for males and females, respectively): Further details mentioned and to be considered in the attached pdf.
2. Reference Vol. 3 (AS) – B.6.5/2, page 298 (not mentioned in Vol. 1 but addressed here as potentially relevant for carcinogenicity evaluation): Further details mentioned and to be considered in the attached pdf.
3. Reference: Vol.1 – level 3, 3.1.9, pages 401 and Vol. 1 – level 2, 2.6.5, page 133: incidence of amyloidosis in carcinogenicity toxicity study in mice: Further details mentioned and to be considered in the attached pdf.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip

Dossier Submitter's Response

Incidence of thyroid c-cell carcinomas HCD: only 1 study among the 40 studies taken from the RITA database had a c-cell carcinoma incidence of 8.3% (25 months duration). The highest incidence after that was 6.0 % (which was actually from a 24 months study).

There were 10 studies in total with a duration of 25-26 weeks. Of these studies 7 of them had an incidence of 2 % or less and 1 had an incidence of 5%. So 8.3% represents the most extreme control group even among the studies of longer duration (25-26 months) and from unknown laboratories and also collected over a time period of 25 years. While we agree that there seem to be no increase in preneoplastic findings and early onset of tumors, there is still a significant trend supporting a dose relationship and a high incidence of tumors in especially the high dose group.

Uterus polyps: This may be a borderline effect. It is a bit unclear if the +/-5 years should be interpreted as 10 year around the study or approximately 2.5 years before and after. The effect on polyps in the study may be borderline, however the incidence in the study is above the HCD (13.3% vs 12%) but just below the upper HCD range if cervix polyps are added to uterus polyps. A mean and Standard Deviation was not calculated from the 29 control groups from 1976-1986 making up the HCD.

Amyloidosis in mice:In humans amyloidosis may in some people be associated with some forms of cancer (multiple myeloma and non-Hodgkin's lymphoma). We are not aware that a link between amyloidosis and carcinogenesis has been esthablished other than, as mentioned, amyloidosis is sometimes seen in people with multiple myeloma or non-Hodgkin's lymphoma.

RAC's response

Thank you very much for your comment. The HCD databases are not ideal. RAC has assessed the reliability of the provided HCD and considered only 2 of them to be valid; specifically, those obtained by the same performing laboratory and within a temporal frame of ±5 years. RAC also concurs with the DS that amyloidosis is not a relevant effect for assessing carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Sweden		MemberState	6

Comment received

We note that there is one additional epidemiological study available in the open literature, which is not mentioned in the CLH report, Lerro et al. 2020, showing association with dicamba use and liver and intrahepatic bile duct cancer that we think should be taken into account in the assessment. (Lerro et al. 2020 Int J Epidemiol; Dicamba use and cancer incidence in the agricultural health study: an updated analysis).

According to the CLP criteria for carcinogenicity "A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data." and for category 1B "In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals." For dicamba, there are animal studies showing limited evidence of carcinogenicity. There are also several human epidemiological studies, with limitations, indicating associations with dicamba and carcinogenicity. We consider that it could be further discussed whether these epidemiological studies could be regarded as limited evidence and consequently together with the animal data warrant a classification of dicamba in category 1B.

Dossier Submitter's Response

Agree that the mentioned study by Lerro and coworkers from 2020 was not included in the CLH report but would be relevant to add for a weight of evidence analysis.

Peroxisome proliferation is mentioned as a possible MOA in the paper, but is also mentioned under mechanisms of tumour formation not considered relevant for humans in the CLP guidance.
RAC's response
Thank you very much for your comment. Noted. RAC has taken into consideration in the assessment the information provided in this study.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	7
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	8
Comment received				
Rotam shares the RMS conclusion that no classification for mutagenicity is required for dicamba. • Vol. 1, 3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS: Rotam is of the opinion that negative results of transgenic rodent study overrules the inconclusive results of comet assay. Comet assays are known to be sensitive for ex vitro false positive results. Any damage of extracted cells will produce tails in electrophoresis. A positive result should be proofed with a TGR test. In case of dicamba ex vivo problems with duodenum cells could not be ruled out with additional investigations. For that reason, the TGR test was conducted to clarify if Comet assay maybe produced a false positive result. Since the TGR test was clearly negative, gene mutation produced by dicamba should be considered unlikely.				
Dossier Submitter's Response				
The TGR test was negative and in our opinon overrules the comet assay which is an indicator test and detect pre-mutagenic lesions, which may not result in mutations. The positive result in duodenum (negative in liver) may be an artefact but this was not proven.				
RAC's response				
Thank you very much for your comment. Noted. RAC notes that the TGR test is relevant for the weight of evidence assessment since it was negative in the duodenum.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	9
Comment received				
Syngenta: Supports the RMS conclusion that no mutagenicity classification is required for dicamba. 1) Reference: Vol. 1 – level 3, page 401 and Vol. 1 – level 2, 2.6.4 pages 114-131 Co-RMS proposed a Muta Cat 2 classification for dicamba due to the duodenum findings in the in vivo Comet assay: Further details mentioned and to be considered in the attached pdf. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Thank you, noted. The TGR test was negative and in our opinon overrules the comet assay which is an indicator test and detect pre-mutagenic lesions, which may not result in mutations. The positive result in duodenum (negative in liver) may be an artefact but this was not proven.				
RAC's response				
Thank you very much for your comment. Please, see responde to comment 8.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	10
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	11
Comment received				
No comment.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	12
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	13
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	14
Comment received				
• Vol. 1, 2.6.2.6, Respiratory sensitisation: Rotam is of the opinion, that based on inhalation toxicity and skin sensitisation data, instead of "No information available", "No evidence of respiratory sensitisation" would be more appropriate.				
Dossier Submitter's Response				
Agree the sentence could be changed.				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	15
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				

Dossier Submitter's Response
Noted
RAC's response
Thank you very much for your comment. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	16
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	17
Comment received				
No comment.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	18
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	19
Comment received				
FR: This section was not reviewed.				

Dossier Submitter's Response
Noted
RAC's response
Thank you very much for your comment. Noted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	20
Comment received				
No comment.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	21
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	22
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	23
Comment received				
No comment.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	24
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	25
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	26
Comment received				
Rotam is of the opinion that the STOT SE 3 H336 classification proposed by the RMS for dicamba is not required. • Vol. 1, 2.6.2.10, Specific target organ toxicity-single exposure (STOT SE): Rotam is of the opinion, that the provided data do not justify a classification for narcotic effects. Data				

are available for exposure of humans to dicamba. In none of them narcotic effects are reported. Dicamba is highly water soluble and substances which lead to narcotic effects are normally fat soluble, a property needed to interact with the central nervous system.
Dossier Submitter's Response
The transient effects observed in several of the dicamba studies like for example ataxia and lethargy may be related to neurotoxicity. In our opinion the criteria for classification as Cat 3 are met: narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. However, this may not be considered enough for classification.
RAC's response
Thank you very much for your comment. Noted. RAC has considered the weight of animal studies versus epidemiological data and concluded that the conditions for classification for STOT SE 3;H336 are met.

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2021	Germany		MemberState	27
Comment received				
STOT SE 3, H335: respiratory effects It is argued on p. 99: „Furthermore, histopathological changes in the lungs found in a 28-day inhalational study indicate local toxicity of dicamba in the respiratory tract that could explain the clinical signs of irritation." However, it is stated in chapter 3.8.2.5 of the guidance: "Category 3 effects should be confined to changes, whether functional or morphological, occurring in the upper respiratory tract (nasal passages, pharynx and larynx)." We concur that the morphological changes reported were seen in the lower respiratory tract. However, functional changes were also reported in all inhalation studies, namely respiratory noise, sneezing, rhinitis and maybe respiratory noise, it is hard to know whether these are necessarily due to an effect in the upper or lower respiratory tract. Interestingly, mottled and partially deflated lungs were also reported the acute exposure study (Kilgour). The evidence indicates that there is an immediate reaction, i.e. sneezing and rhinitis as the body tries to get rid of the substance and once it gets into the lower respiratory tract it causes morphological changes, these presumably taking somewhat longer manifest. The DE CA supports STOT SE 3, H335 but a case could potentially also be made for STOT RE.				
Dossier Submitter's Response				
Thank you for the input. We agree with the comment made by Germany.				
RAC's response				
Thank you very much for your comment. Noted. RAC concluded that the conditions for classification for STOT SE 3;H335 are met. RAC also supported the DS proposal for no classification for STOT RE.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	28
Comment received				
Specific target organ toxicity – single exposure: Syngenta considers classification of dicamba for STOT SE - narcotic effects Cat 3 as not required and for STOT SE – respriatory irritation as questionable. 1. Reference Vol. 1 – level 2, 2.6.10.2 and 2.6.2.10.3, pages 99-100: RMS proposes				

STOT SE 3 H336 (may cause drowsiness or dizziness) and H335 (may cause respiratory tract irritation): Further details mentioned and to be considered in the attached pdf. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip
Dossier Submitter's Response
STOT SE 3 H336: The transient effects like ataxia and lethargy may be related to neurotoxicity. In our opinion the criteria for classification as Cat 3 are met. STOT SE 3 H335:In our opinion the findings in the animals studies (respiratory tract irritation and histopathological changes) are severe enough to meet the classification criteria.
RAC's response
Thank you very much for your comment. Noted. RAC has considered the weight of all the available evidence and supported the DS proposal for classification for both these endpoints.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	29
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	30
Comment received				
No comment.				
Dossier Submitter's Response				
RAC's response				

Date		Country	Organisation	Type of Organisation	Comment number
09.06.2021		Germany		MemberState	31
	Comment received				
	It can be taken from table 23, that three studies detected effects at doses below the guidance values for STOT RE classification. 1: The study on developmental toxicity in rats showed lethality (4/25 deaths) at 400 mg/kg bw/day. The dose is below the guidance value after extrapolation, but lethality occurred quite early at gd 7 & 8 and could be considered as an acute effect. 2: The study on developmental toxicity in rabbits showed e.g. 4/20 abortions as maternal toxicity at 300 mg/kg bw/day. After duration adjustment this dose is also below the guidance value. It could be added, whether the abortions occurred very early, implying an acute effect or later in the study, what would indicate an effect after repeated exposure. 3: With regard to the 28 d-inhalation study in rats it is stated on p. 114: „For the inhalation study (2014) was the extrapolated effective dose below the guidance values for STOT-RE, however, the effect at this dose was only seen on bw gain and not mean body weight." It is not clear, what dose is meant, but at the LOAEC of 0.005 mg/L, mentioned in table 23, minimal multifocal bronchiolo-alveolar hyperplasia in 2/10 males is described on p. 107, but no effect on bw gain. The highest dose of 0.05 mg/L corresponds to a dose of 0.016 mg/L after duration adjustment, which is even below the guidance values for STOT RE 1 (0.02 mg/L). This and the corresponding effects should be discussed in more detail.				
	Dossier Submitter's Response				
	Thank you for pointing these effects out. Agree with Germany that these effects may be considered relevant for classification.				
	RAC's response				
	Thank you very much for your comment. Noted. RAC has discussed the possibility of a STOT RE classification but supported the DS proposal for no classification for STOT RE.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	32
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Thank you very much for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	33
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you very much for your comment. Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
09.06.2021	Germany		MemberState	34
Comment received				

• General
Study summaries: Please add a short section at the end of each study summary, stating whether the study is valid, reliable, and suitable for classification purposes.
• Fate and behaviour in the environment
We are not sure if Table 66 on page 201 in Volume 1 should also include the results of the aquatic simulation tests, hydrolytic degradation and aqueous photochemical degradation. At least in regard to the mineralization measured in the studies (because of the hint "* data on full mineralization should be reported"). We miss a short conclusion. What do the described results of the single degradation in water studies mean in regard to rapid degradation?
• Effects on non-target organisms
Toxicity to algae:
Please clarify and update the information on the key study for acute aquatic hazard. In Table 73, an EC50 (120 h) of 0.58 mg a.s./L for Skeletonema costatum is shown, originating from the study by Hoberg (1993). However, this 120 h EC50 is not reported in the respective study summary on pages 226f. Furthermore, in table 74 it is reported that the most sensitive EC50 originates from the study on Navicula pelliculosa by Hoberg (1992), which conflicts with the information given in Table 73. Please clarify which study/species was relevant for the classification of acute aquatic hazard, correct the information in the respective tables, and give further information on the 120 h EC50 in the study summaries.

In Table 72 on page 220, the study by Hoberg (1993) is marked as supportive information only. If this is the case, why was the endpoint from this study used for classification? We see diatoms are sensitive to dicamba, so it would make sense to use an endpoint from a study on this organism group. However, studies should still be of sufficient quality to be used for classification. Please provide a rationale why this study was used for classification purposes.

Please provide further information on the NOEC for Skeletonema costatum based on the endpoint growth rate. Is it equal to the reported NOEbC of 0.011 m a.s./L reported on page 227? In general, classification should be based on the endpoint growth rate rather than biomass.

The table in the study summary on page 227 only indicates statistically significant differences for the 120 h data. From the look of it, the reduction in cell density should

also be significant (at least at some test concentrations) at 72 and 96 h. Please check if this is the case and, if necessary, update the table accordingly.

Classification:
We agree with the classification not rapidly degradable.
We also agree that the active substance dicamba is not bioaccumulative.
At the moment it is not clear if the EC50 of 0.58 mg a.s./L from Hoberg (1993) is actually a reliable endpoint that can be used for classification purposes. However, the study by Kirkwood (2015) on Myriopyllum spicatum provides an ErC50 of 0.94 mg a.s./L. This is also between 0.1 and 1 mg/L and would lead to the same classification as Aquatic Acute 1 with M-factor 1. We therefore agree with the proposed acute aquatic hazard classification.

Currently it is not clear if the study by Hoberg (1993) and its resulting NOEC of 0.011 mg a.s./L should be used for classification purposes. The next lowest NOEC is 0.27 mg a.s./L for Myriophyllum spicatum (Kirkwood 2015). Based on this endpoint, the active substance dicamba would be classified as "Aquatic Chronic 2" instead of "Aquatic Chronic 1". Please provide further information if the endpoint from Hoberg (1993) is suitable for classification, or correct the classification accordingly.

Dossier Submitter's Response

Proper study evaluations are provided in the RAR Volume 3 B9 Ecotoxicology, incl. statements on the reliability of each study. The studies by Hoberg (1992b) and Hoberg (1993) are not considered valid, because the studies do not fulfil all the validity criteria of the current OECD TG 21. Data from these studies are considered supportive information only. Thus endpoints from these studies cannot be used for classification purposes.

We belive that table 66 on page 201 should present the OECD 301 tests (ready biodegradability). A short conclusion on ready biodegradability is given below the table under point 2.8.2.1.1.

According to Annex 4.1.2.7.1 in the ECHA guidance on CLP, EC_{50}s from aquatic plants growth tests should be treated as acute values for classification purposes. Therefore most sensitive acute endpoint for dicamba technical is the E_rC_{50} of 0.94 mg a.s./L for *M. spicatum*. As E_rC_{50} is ≤1 mg/L, dicamba is assessed as Aquatic Acute Category 1 and assigned a M factor of 1.

The most sensitive chronic endpoint is NOEC of 0.27 mg a.s./L for *M. spicatum* originating from the study by Kirkwood, 2015 (with estimated Er_r50 of 0.94 mg a.s./L and E_rC20 of 0.35 mg a.s./L). Considering that dicamba is not readily degradable and NOEC is ≤1 mg/L, dicamba should be classified as Aquatic Chronic Category 2, thus labelled with H411.

RAC's response

The study with *Lemna gibba* was not conducted according to current guideline (OECD 221) and differed from that guideline in several aspects, including study duration (14 d instead of 7 d). Consequently, the study with *Myriophyllum spicatum* conducted according to current guideline (OECD 221) is considered more robust. As the results of these two studies are quite similar, RAC agrees with the DS responses concluding for a Aquatic Chronic Category 2.

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2021	Netherlands		MemberState	35

Comment received

Ecotoxicity, degradation and bioaccumulation

General comments
We cannot agree with the proposed adaptation for C&L. Insufficient information has been provided to be able to conclude on the environmental hazard classes. The Dosier Submitter is therefore requested to provide additional information. Please see the specific comments, below.

Specific comments
p. 226-227 - The key study used for the acute and chronic classification (Hoberg 1993; SAN837/5224) has not been summarised in sufficient detail to be able to assess the validity of the information presented. The summaries lack detailed information on the methodology (test substance preparation, replication, initial cell density, water quality parameters, GLP-compliance, etc.) and results (cell densities at 24 and 48 h, validity criteria, tabulated results on growth rates, etc). The Dossier Submitter is therefore requested to provide a more extensive summary to enable insight in the proposed C&L adaptation.

Furthermore, the 120-h ErC50 value of 0.58 mg/L used for the acute classification is not mentioned. It is also unclear as to why this value has been used specifically for the acute classification. The endpoint should be derived at 72 or 96 hours, unless the available raw data show monotone exponential growth of the controls also at a longer time point (in this case 120 h), as described in the REACH Guidance chapter R.7.8.4.1. Thus, if 120-h values are used, these should be justified by the Dossier Submitter.

Also, according to the summary, the value used for the chronic classification (0.011 mg/L) seems to the 72-h NOEC derived based on biomass as indicated by 'NOEbC'. It should be noted that an EC10 value based on growth rate (ErC10) is the preferred endpoint for environmental chronic classification purposes. Could the Dossier Submitter provide endpoints based on growth rate?

p. 230 – In Table 74, the lowest effect value for algae (0.58 mg/L) is indicated to be derived from the Hoberg 1992a study on freshwater algae (N. pelliculosa). However, this value is previously reported to be derived from the Hoberg 1993 study on marine algae (S. costatum). The Dossier Submitter is requested to clarify this inconsistency.

Dossier Submitter's Response

Study details and study evaluations are provided in the RAR Volume 3 B9 Ecotoxicology, incl. statements on the reliability of each study. The studies by Hoberg (1992b) and Hoberg (1993) are not considered valid, however, considered supportive information only. Thus endpoints from these studies cannot be used for classification purposes.

According to Annex 4.1.2.7.1 in the ECHA guidance on CLP, EC_{50}s from aquatic plants growth tests should be treated as acute values for classification purposes. Therefore most sensitive acute endpoint for dicamba technical is the E_rC_{50} of 0.94 mg a.s./L for *M. spicatum*. As E_rC_{50} is ≤1 mg a.s./L, dicamba is assessed as Aquatic Acute Category 1 and assigned a M factor of 1.

The most sensitive chronic endpoint is NOEC of 0.27 mg a.s./L for *M. spicatum* originating from the study by Kirkwood, 2015 (with estimated Er_r50 of 0.94 mg a.s./L and E_rC20 of 0.35 mg a.s./L). Considering that dicamba is not readily degradable and NOEC is ≤1 mg/L, dicamba should be classified as Aquatic Chronic Category 2, thus labelled with H411.

The E_rC50 value of 0.58 mg/L indicated in Table 74 in the CLH report orginates from the study by Hoberg 1993 (and not from Hoberg, 1992 as presently indicated in the table). The reference details can be revised in an updated CLH report. This will not change the outcome of the proposed classification.

RAC's response

The study with *Lemna gibba* was not conducted according to current guideline (OECD 221) and differed from that guideline in several aspects, including study duration (14 d instead of 7 d). Consequently, the study with *Myriophyllum spicatum* conducted according to current guideline (OECD 221) is considered more robust. As the results of these two studies are quite similar, RAC agrees with the DS responses concluding for a Aquatic Chronic Category 2.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	36

Comment received

FR: The acute and chronic classification proposed by RMS are based on the study of Hoberg (1993) SAN837/5224 on Skeletonema costatum. According to the RAR Vol 3 (AS) of dicamba - Draft RAR updated version December 2020 – this study is considered as "supplementary data" by the RMS as "the study only fulfils two of the three validity criteria of the current OECD 201 guideline".
Therefore, since the study is not valid, then endpoint from this study should not be used for the proposal classification of dicamba. Based on this point, as a general remark it is FR opinion that only valid studies should be reported in the CLH report in order to propose a classification based on valid endpoints. Could RMS update CLH report accordingly?

Therefore, based on available valid studies from Draft RAR updated version December 2020, FR considered that the lowest relevant endpoints available are from the study of Kirkwood A. (2015) on Myriophyllum spicatum with an ErC50 value of 0.94 mg as/l and a NOErC value of 0.27 mg as/L.
Based on these endpoints and by considering dicamba as not readily biodegradable, the acute classification cat. 1 with a M-factor 1 and the chronic classification cat 2 should be retained for dicamba. Could RMS update CLH report accordingly?

Dossier Submitter's Response

We agree that endpoints used for classification purposes should originate from studies considered valid and reliable. As the study by Hoberg (1993) is not considered valid, endpoints from this study cannot be used for classification of dicamba. We recognize that the CLH report could be updated to only include endpoints originating from studies that are considered valid and reliable.

We agree that the most sensitive endpoints to be used for classification of dicamba are E_rC_{50} of 0.94 mg a.s./L for acute toxicity and NOEC of 0.27 mg a.s./L for chronic toxicity (both values originating from the study by Kirkwood, 2015). As a result dicamba should be classified as Aquatic Acute Category 1 (with a M factor of 1) and Aquatic Chronic Category 2 (as dicamba is not rapidly degradable).

RAC's response
The study with *Lemna gibba* was not conducted according to current guideline (OECD 221) and differed from that guideline in several aspects, including study duration (14 d instead of 7 d). Consequently, the study with *Myriophyllum spicatum* conducted according to current guideline (OECD 221) is considered more robust. As the results of these two studies are quite similar, RAC agrees with the DS responses concluding for a Aquatic Chronic Category 2.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	United Kingdom	Health and Safety Executive	National Authority	37

Comment received
Dicamba (EC: 217-635-6; CAS: 1918-00-9) We agree that algae and aquatic plants are the most sensitive trophic level based on the available ecotoxicity data. Aquatic Acute Classification The proposed aquatic acute classification is based on a mean measured 120-hour ErC50 of 0.58 mg a.s./L for Skeletenoma costatum. We note a 72-hour ErC50 endpoint of >4.1 mg a.s./L (mean measured) is also available. Is there information to consider that a 120-hour endpoint should be used in preference to the 72-hour endpoint which is the standard duration used for hazard classification (ECHA, 2017)? If not, we consider the 72-hour endpoint is more appropriate for hazard classification. Considering the 72-hour ErC50 for Skeletenoma costatum, the lowest acute toxicity endpoint may be the 14-day ErC50 of 0.94 mg a.s./L for Myriophyllum spicatum. This endpoint results in the same Aquatic Acute 1 classification with an M-factor of 1. Aquatic Chronic Classification The proposed aquatic chronic classification is based on the 72-hour NOEbC of 0.011 mg a.s./L for Skeletenoma costatum. We note that growth rate endpoints are preferred over biomass endpoints for the purpose of hazard classification and where available, ECx values should also be used instead of NOEC values (ECHA, 2017). The RAR includes a reliable mean measured 72-hour ErC10 of 0.440 mg/L for this study, in addition to ErC10 values for other durations. As above, is there any reason to consider 120-hour endpoints preferable for this species? If not, we consider the 72-hour EC10 endpoint is more appropriate for hazard classification Noting the 72-hour ErC10 for Skeletenoma costatum is not the most chronically sensitive endpoint, the lowest reliable chronic toxicity endpoints are the Myriophyllum spicatum 14-day NOErC of 0.27 mg/L and ErC20 of 0.35 mg a.s./L (initial measured) based on shoot length. Reliable ErC10 values could not be determined for this study. The ErC20 from this study is obtained from the RAR and should be used in preference to the NOErC. These chronic endpoints are in the range from >0.1 to ≤1 mg/L, which result in an Aquatic Chronic 2 classification given that dicamba is considered not rapidly degradable. We note the Lemna gibba 14-day NOErC = 0.19 mg/L (mean measured) based on frond number is also within this concentration range. Is it possible to determine 7-day ECx

endpoints for this study in line with the standard duration of Lemna endpoints used for hazard classification (ECHA, 2017)?

ECHA (2017). Guidance on the application of the CLP criteria. Version 5.0. Helsinki: ECHA.

Dossier Submitter's Response

The studies by Hoberg (1992b) and Hoberg (1993) are not considered valid, however, considered supportive information only. Thus endpoints from these studies cannot be used for classification purposes.

According to Annex 4.1.2.7.1 in the ECHA guidance on CLP, EC_{50}s from aquatic plants growth tests should be treated as acute values for classification purposes. Therefore most sensitive acute endpoint for dicamba technical is the E_rC_{50} of 0.94 mg a.s./L for *M. spicatum*. As E_rC_{50} is ≤1 mg/L, dicamba is assessed as Aquatic Acute Category 1 and assigned a M factor of 1.

The most sensitive chronic endpoint is NOEC of 0.27 mg a.s./L for *M. spicatum* originating from the study by Kirkwood, 2015 (with estimated Er_r50 of 0.94 mg a.s./L and E_rC20 of 0.35 mg a.s./L). Considering that dicamba is not readily degradable and NOEC is ≤1 mg/L, dicamba should be classified as Aquatic Chronic Category 2, thus labelled with H411.

Wrt. *L. gibba* study by Hoberg (1992c), statistically re-analysis of data was undertaken by Taylor (2015e). Calculated E_rC_{50} For *L. gibba* was >3.2 mg a.s./L, whereas valid EC_{10} and EC_{20} values were not determinable. These data were not used for classification of dicamba.

RAC's response

The study is considered acceptable as supplementary data. The study is considered valid according to the original guideline and the re-analysis of data to yield 72-hour E_rC_{50} and E_bC_{50} values is considered valid. However, the study only fulfils two of the three validity criteria of the current OECD 201 guideline
The study with *Lemna gibba* was not conducted according to current guideline (OECD 221) and differed from that guideline in several aspects, including study duration (14 d instead of 7 d). Consequently, the study with *Myriophyllum spicatum* conducted according to current guideline (OECD 221) is considered more robust. As the results of these two studies are quite similar, RAC agrees with the DS and MS proposal concluding for a Aquatic Chronic Category 2.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	38
Comment received				
No comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	39

Comment received

The RMS proposed classification for Dicamba is Aquatic Acute Cat. 1 (H400) and Aquatic Chronic Cat. 1 (H410).
This classification is based on an algae study with the test species Skeletonema costatum (Hoberg, 1993). In the RAR (Volume 3CA B9 pag.94), the RMS considered this study acceptable only as supplementary data. The study does not fulfil the validity criteria of the current OECD 201 guideline: In fact the mean section-by-section specific growth rate CV was 48% (must be ≤ 35%) This was clearly highlighted by the RMS in Volume 3CA B9 pag.94. Due to this reason, the study should be considered as not valid and should not be considered for classification and risk assessment purposes. Moreover, according to Regulation 1272/2008, the 96h endpoints from algae studies must be considered for classification, whereas the proposal by the dossier submitter considered the 120h endpoint from this invalid study. Thus, even if the study would fulfil the validity criteria the results of this study would not justify the proposed classification. Syngenta kindly asks to correct the environmental classification proposal considering that the study that leads to the current proposal is not valid according to the current OECD guideline and the incorrect endpoint was selected for classification proposal.
Acute aquatic hazard [equivalent to section 11.5 of the CLH report template]
Considering that the algae study with Skeletonema costatum (Hoberg, 1993) is not valid, the lowest relevant LC50/EC50 for fish, daphnia and algae is > 1 mg/L.
Thus, Dicamba should not be classified as acute hazardous to the aquatic environment.

Long-term aquatic hazard [equivalent to section 11.6 of the CLH report template]
Considering that the algae study with Skeletonema costatum (Hoberg, 1993) is not valid, the most sensitive species group to chronic exposure to dicamba was Myriophyllum spicatum (Kirkwood, 2015; 14-day NOEC = 0.27 mg/L).
Considering this endpoint and that Dicamba is not rapidly degradable, the following classification should be warranted: Aquatic Chronic Cat.2 (H411).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip

Dossier Submitter's Response

The studies by Hoberg (1992b) and Hoberg (1993) are not considered valid, however, are considered supportive information only. Thus endpoints from these studies cannot be used for classification purposes.

According to Annex 4.1.2.7.1 in the ECHA guidance on CLP, EC_{50}s from aquatic plants growth tests should be treated as acute values for classification purposes. Therefore most sensitive acute endpoint for dicamba technical is the E_rC_{50} of 0.94 mg a.s./L for *M. spicatum*. As E_rC_{50} is ≤1 mg/L, dicamba is assessed as Aquatic Acute Category 1 and assigned a M factor of 1.

We agree that the most sensitive chronic endpoint is NOEC of 0.27 mg a.s./L for *M. spicatum*. As dicamba is not readily degradable and NOEC is ≤1 mg/L, dicamba should be classified as Aquatic Chronic Category 2, thus labelled with H411.

RAC's response
The study with *Lemna gibba* was not conducted according to current guideline (OECD 221) and differed from that guideline in several aspects, including study duration (14 d instead of 7 d). Consequently, the study with *Myriophyllum spicatum* conducted according to current guideline (OECD 221) is considered more robust. As the results of these two studies are quite similar, RAC agrees with the DS responses concluding for a Aquatic Chronic Category 2.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	40
Comment received				
No comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	41
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	42
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	Spain	Rotam Agrochemical Europe Limited	Company-Downstream user	43
Comment received				
No comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2021	Austria	Syngenta	Company-Manufacturer	44
Comment received				
No comment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2021	France		MemberState	45
Comment received				
FR: This section was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. Dicamba - ECHA Public consultation_Syngenta comments + docs_Redacted.zip [Please refer to comment No. 2, 5, 9, 12, 15, 18, 21, 24, 28, 32, 39, 41, 44]