Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

proquinazid (ISO); 6-iodo-2-propoxy-3-propylquinazolin-4(3*H*)-one

EC Number: -
CAS Number: 189278-12-4

CLH-O-0000007362-77-01/F

Adopted

14 September 2023

P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 6-IODO-2-PROPOXY-3-PROPYLQUINAZOLIN-4(3H)-ONE;PROQUINAZID (ISO)

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: proquinazid (ISO); 6-iodo-2-propoxy-3-propylquinazolin-4(3H)-one;
EC number: -
CAS number: 189278-12-4
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	1
Comment received				
Applicant agrees with the proposed Classification which is identical to the current harmonised classification. Complimentary to the comments provided via online form, applicant, Applicant (Corteva Agriscience) would like to provide further and more detailed comments to address specific datapoints and discussions provided in the CLH Report & its annexes (correspondence to: Vol 1 and Vol 3 of the Combined Draft Renewal Assessment Report prepared according to Regulation (EC) N° 1107/2009 and Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008)). Within this attachements applicant would like to address other classification discussions (such as P, POP/vPvB, PBT, ED) but not part of the hazard classes open for public consultation. In summary applicant believes that proquinazid does not fulfills any of the classification criterias for P, POP, vPvB, PBT, ED on the basis of the available and newly generated data that applicant would like to provide upon request, prior to RAC evaluation. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				
Dossier Submitter's Response				
Noted. Regarding the comments in the applicant's attached document, the DS have provided detailed responses and proposals for requirements of additional data and expert				

consultations, within the scope of the peer review of the Renewal Assessment Report of Proquinazid (AIR IV) (EFSA-Q-2018-00520). A copy of that reporting table can be provided on request, if not already available to the RAC, but the final outcome of that peer review is still pending.
RAC's response
Thank you, noted. Those comments in the attached form that are related to Vol. 1 (i.e. the CLH report) are addressed under the respective hazards.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	2
Comment received				
No comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2023	Germany		MemberState	3
Comment received				
Overall, we support the proposal of the Swedish authority to keep the current (2011) classification of proquinazid. We suggest, however, to take into account our specific comments related to phototoxicity, photomutagenicity and the presumably human-relevant liver toxicity.				
Dossier Submitter's Response				
Noted, thank you.				
RAC's response				
Thank you, noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	4
Comment received				
Applicant is in support of the RMS proposal for Carc. Cat 2. Classification, which is in alignment with the current ECHA harmonised classification. In further support of this position the Applicant has generated additional information (Study ID: 220243) on the mode of action and human relevance which is relevant to the CLH assessment for carcinogenicity. The additional data is also relevant to the endocrine conclusion, as the data supports the proposed liver-thyroid mode of action and demonstrates non-human relevance. Study report is due to finalisation (end March 2023) The study report and a position paper addressing the impact of the new data on the endocrine and carcinogenicity assessments will be provided upon request: • In vitro CYP and UGT induction and cell proliferation in Sprague-Dawley rat and human hepatocytes by X11166670 (Study ID: 220243) • Position paper addressing the impact of the new data on the CLH carcinogenicity				

assessments and endocrine conclusion

Briefly, the Applicant has conducted comparative species (rat and human) liver enzyme and hepatocyte cell proliferation studies. Whilst there is no defined test guideline for these assays, they were conducted based on published procedures, and the liver enzyme assays are in line with the ECHA-EFSA ED guidance document Appendix A.
The results of the comparative liver enzyme study demonstrate a clear quantitative difference between the differential (delta) UGT-T4 activity levels of rat and human hepatocytes after administration of proquinazid. Human hepatocytes require approximately 100 times higher concentration of proquinazid to see the same limited effect on UGT-T4 activity as observed in the rat; concentration above that limited effect level produce cytotoxicity in human hepatocytes. Given that the follicular changes in the rat thyroid are likely driven by T4-UGT induction (with resulting increased TH turnover) and the clear difference between rats and humans with regards to UGT-T4 induction, the thyroid changes observed in rats are likely not relevant to humans at plausible exposure scenarios and thus support the non-human relevance for the thyroid tumours observed in rats.
With regards to the comparative hepatocyte proliferation assay (report ID: 220243), no proliferative effects were seen in rat hepatocytes (consistent with 7d findings in the 2yr rat carcinogenicity study), and no proliferation in human hepatocytes (positive controls in both species performed as expected). The Applicant considers this important to the CLH classification assessment with regards to the liver tumours, indicating these have non-human relevance.
Overall, these results when considered as a part of the endocrine and carcinogenicity assessment support a rodent specific mode of action that is not relevant to humans.
Furthermore, the Applicant would like to provide detailed comments on the annexes of the CLH dossier in parallel with those submitted under Call for comments on the Renewal Assessment Report of Proquinazid (AIR IV) and relevant to the carcinogenicity hazard assessment, which also lists the new information generated and will be made available for RAC review, upon request. Due to the size and context this is being provided as an attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf

Dossier Submitter's Response

Noted. The DS would welcome the data mentioned by the applicant, related to observed liver and thyroid effects, and have proposed that EFSA request this as additional data in the peer review of the Renewal Assessment Report of Proquinazid (AIR IV) (EFSA-Q-2018-00520). Regarding the comments in the applicant's attached document, see comment 1.

RAC's response

Thank you for your comments. RAC agrees to retain Carc. 2.
The main carcinogenic finding is liver tumours in female rats (hepatocellular adenomas, cholangiocarcinomas). There is no indication that these are not relevant for humans. Data on cell proliferation say nothing about human relevance in this case: no increase in hepatocyte BrdU labelling index was observed in top dose rats at 7 days in the 2-year study, and yet 35 out of 61 of females eventually developed liver neoplasms (compared to 1 animal in the control).

RAC agrees that the increase in hepatocellular carcinomas in male mice is rather weak and not statistically significant. Of note is, however, that a pattern of liver toxicity similar to that in female rats was seen in both sexes of mice (hepatocyte hypertrophy, hepatocyte alteration, oval cell hyperplasia, necrosis). Thyroid adenomas provided additional support for classification.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	5
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2023	Germany		MemberState	6
Comment received				
No comments. We fully support the dossier submitter's proposal to maintain the current classification "Carc 2 – H351" for proquinazid.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Thank you for your comment. RAC agrees to retain Carc. 2.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	7
Comment received				
The Applicant is in support of the RMS proposal for no genotoxicity/mutagenicity classification required, which is in alignment with the current ECHA harmonised classification. All available data confirms that no genotoxicity concerns for proquinazid. Furthermore, the Applicant would like to provide detailed comments on the annexes of the CLH dossier in parallel with those submitted under Call for comments on the Renewal Assessment Report of Proquinazid (AIR IV) and relevant to the mutagenicity hazard assessment, which also lists the new information generated and will be made available for RAC review, upon request. Due to the size and context this is being provided as an attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				

Dossier Submitter's Response
Noted. Regarding the comments in the applicant's attached document, see comment 1.
RAC's response
Thank you, your support for no classification is noted. RAC agrees that there are several lines of evidence indicating that bone marrow was exposed in the two *in vivo* micronucleus assays dated 1999. RAC also notes that some of the deviations from test guidelines listed in the CLH report, tables 2.6.4-1. and 2.6.4-2., are in fact not deviations.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	8
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2023	Germany		MemberState	9
Comment received				
We agree that there was no evidence from the available studies that proquinazid might be genotoxic. However, a positive in vitro test for phototoxicity (as is the case here) may trigger a need for investigation of photomutagenicity under different sectorial regulations such as the PPPR. This should be acknowledged. Classification for germ cell mutagenicity is not impacted though.				
Dossier Submitter's Response				
Noted, thank you.				
RAC's response				
Thank you, your support for no classification is noted. The positive phototoxicity test might trigger further investigations but this has indeed no impact on the current classification process.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	10
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	11
Comment received				
Applicant is in support of the RMS proposal for no reproductive toxicity classification required, which is in alignment with the current ECHA harmonised classification. All available data confirms that no reproductive toxicity concerns for proquinazid. Furthermore, the Applicant would like to provide detailed comments on the annexes of the CLH dossier in parallel with those submitted under Call for comments on the Renewal Assessment Report of Proquinazid (AIR IV) and relevant to the reproductive toxicity hazard assessment, which also lists the new information generated and will be made available for RAC review, upon request. Due to the size and context this is being provided as an attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				
Dossier Submitter's Response				
Noted. Regarding the comments in the applicant's attached document, see comment 1.				
RAC's response				
Thank you, your support for no classification is noted. RAC agrees that increased incidence of patent ductus arteriosus observed *in utero* may represent a developmental delay. RAC notes that the incidences of delayed ossification in the rat and rabbit PNDT studies remained within the HCD range. The increases may still be related to treatment. Nevertheless, delayed ossification does not normally lead to classification.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	12
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	13
Comment received				
Applicant agrees with the RMS conclusion for proquinazid does not fulfil criteria for classification for acute oral toxicity according to Regulation (EC) No. 1272/2008. Applicant agrees with the RMS conclusion for proquinazid does not fulfil criteria for				

classification for acute dermal toxicity according to Regulation (EC) No. 1272/2008. Applicant agrees with the RMS conclusion for proquinazid does not fulfil criteria for classification for acute inhalation toxicity according to Regulation (EC) No. 1272/2008. Furthermore, the Applicant would like to provide detailed comments on the annexes of the CLH dossier in parallel with those submitted under Call for comments on the Renewal Assessment Report of Proquinazid (AIR IV) and relevant to the acute toxicity hazard assessment, which also lists the new information generated and will be made available for RAC review, upon request. Due to the size and context this is being provided as an attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf
Dossier Submitter's Response
Noted. Regarding the comments in the applicant's attached document, see comment 1.
RAC's response
Thank you, noted.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	14
Comment received				
Applicant agrees with the RMS conclusion for proquinazid does not fulfil criteria for classification for skin corrosion/irritation according to Regulation (EC) No. 1272/2008. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				
Dossier Submitter's Response				
Noted. Regarding the comments in the applicant's attached document, see comment 1.				
RAC's response				
Thank you, noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	15
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2023	Germany		MemberState	16
Comment received				
In the case of this substance, there is evidence of phototoxicity. This finding points to the fact that, to date, there is no adequate reflection of such properties in the current classification system of chemicals.				
Dossier Submitter's Response				
Noted, thank you.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	17
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	18
Comment received				
Applicant agrees with the RMS conclusion for proquinazid does not fulfil criteria for classification for serious eye damage/eye irritation according to Regulation (EC) No. 1272/2008. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				
Dossier Submitter's Response				
Noted. Regarding the comments in the applicant's attached document, see comment 1.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	19
Comment received				
Was not reviewed.				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	20
Comment received				
Applicant agrees with the RMS conclusion for proquinazid does not fulfil criteria for classification for according to Regulation (EC) No. 1272/2008. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				
Dossier Submitter's Response				
Noted. Regarding the comments in the applicant's attached document, see comment 1.				
RAC's response				
Thank you, noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	21
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	22
Comment received				
Applicant agrees with the RMS conclusion for proquinazid does not warrant classification as Specific Target Organ Toxicity – Single Exposure according to Regulation (EC) No. 1272/2008. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf
Dossier Submitter's Response
Noted. Regarding the comments in the applicant's attached document, see comment 1.
RAC's response
Thank you, noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	23
Comment received				
Applicant agrees with the RMS conclusion for proquinazid does not meet the criteria for classification as STOT RE according to Regulation (EC) No. 1272/2008; and the MoA of adverse thyroid effects in rats is considered rodent specific, and therefore not relevant to humans. In further support of this position the Applicant has generated additional information (Study ID: 220243) on the mode of action and human relevance which is relevant to the CLH assessment for carcinogenicity. The additional data is also relevant to the endocrine conclusion, as the data supports the proposed liver-thyroid mode of action and demonstrates non-human relevance. Study report is due to finalisation (end March 2023) The study report and a position paper addressing the impact of the new data on the endocrine and carcinogenicity assessments will be provided upon request: • In vitro CYP and UGT induction and cell proliferation in Sprague-Dawley rat and human hepatocytes by X11166670 (Study ID: 220243) • Position paper addressing the impact of the new data on the CLH carcinogenicity assessments and endocrine conclusion Briefly, the Applicant has conducted comparative species (rat and human) liver enzyme and hepatocyte cell proliferation studies. Whilst there is no defined test guideline for these assays, they were conducted based on published procedures, and the liver enzyme assays are in line with the ECHA-EFSA ED guidance document Appendix A. The results of the comparative liver enzyme study demonstrate a clear quantitative difference between the differential (delta) UGT-T4 activity levels of rat and human hepatocytes after administration of proquinazid. Human hepatocytes require approximately 100 times higher concentration of proquinazid to see the same limited effect on UGT-T4 activity as observed in the rat; concentration above that limited effect level produce cytotoxicity in human hepatocytes. Given that the follicular changes in the rat thyroid are likely driven by T4-UGT induction (with resulting increased TH turnover) and the clear difference between rats and humans with regards to UGT-T4 induction, the thyroid changes observed in rats are likely not relevant to humans at plausible exposure scenarios and thus support the non-human relevance for the thyroid tumours observed in rats. With regards to the comparative hepatocyte proliferation assay (report ID: 220243), no proliferative effects were seen in rat hepatocytes (consistent with 7d findings in the 2yr rat carcinogenicity study), and no proliferation in human hepatocytes (positive controls in both species performed as expected). The Applicant considers this important to the CLH classification assessment with regards to the liver tumours, indicating these have non-human relevance. Overall, these results when considered as a part of the endocrine and carcinogenicity				

assessment support a rodent specific mode of action that is not relevant to humans Furthermore, the Applicant would like to provide detailed comments on the annexes of the CLH dossier in parallel with those submitted under Call for comments on the Renewal Assessment Report of Proquinazid (AIR IV) and relevant to the STOT-RE hazard assessment, which also lists the new information generated and will be made available for RAC review, upon request. Due to the size and context this is being provided as an attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf
Dossier Submitter's Response
Noted. The DS would welcome the data mentioned by the applicant, related to observed liver and thyroid effects, and have proposed that EFSA request this as additional data in the peer review of the Renewal Assessment Report of Proquinazid (AIR IV) (EFSA-Q-2018-00520). Regarding the comments in the applicant's attached document, see comment 1.
RAC's response
Thank you for your comments. RAC concluded that a STOT RE classification for the liver and thyroid is justified. See response to comment no. 25.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	24
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2023	Germany		MemberState	25
Comment received				
We agree that the missing information for an in vitro study of enzyme activity with human hepatocytes constitutes a data gap and that all requirements of the ED guidance should generally be fulfilled when thyroid disruption in experimental animals is evaluated for its human relevance. Still, there seems to be rather convincing evidence that thyroid toxicity of proquinazid in rodents is, most likely, due to a mode of action of limited quantitative relevance to man. However, human relevance of liver toxicity cannot be excluded. The argumentation against classification put forward by the DS is partly based on the assumption of adaptive changes and partly on the consideration of liver findings to preceed liver tumours, i.e., they were regarded as pre-neoplastic lesions. We agree that "double classification" should be avoided. However, in case that proquinazid should not be classified for carcinogenicity				

(in contrast to the DS proposal that we support), STOT RE 2 (liver) should be considered.
Dossier Submitter's Response
Noted. The DS agrees that that thyroid toxicity of proquinazid in rodents is, most likely, of limited quantitative relevance to man, but have proposed that EFSA request additional data regarding the relevant mode of action, see comment 23. Furthermore, the DS agrees that STOT RE 2 (liver) classification should be considered, if the current carcinogenicity classification is not maintained.
RAC's response
Liver: RAC agrees with the DS that increases in liver weight and hepatocellular hypertrophy observed in studies with proquinazid below the GVs may be adaptive and are not sufficient for classification. Further, oval cell hyperplasia is related to liver tumours and is therefore covered by the existing classification as Carc. 2. However, relation to carcinogenicity of alteration/degeneration of hepatocytes and microvesicular fatty change is unclear. Both lesions are considered adverse and occurred at dose levels relevant for classification. Therefore, in contrast to the previous assessment, RAC now proposes to add classification in Category 2 for the liver. Thyroid: RAC agreed on classification in Category 1 for the thyroid based on the following arguments: • Effects were observed below the GV for Category 1. • UGT induction was observed in human hepatocytes. This confirms human relevance of UGT-related thyroid findings in rats. • Thyroid effects in rats generally started at lower doses than liver effects. Thus, liver enzyme induction is not the main MoA of thyroid effects. • Both UGT induction and deiodinase inhibition are relevant for humans and are adverse to offspring development.

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	26
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	27
Comment received				
Applicant agrees with the RMS conclusion for proquinazid does not fulfil criteria for classification for aspiration hazard according to Regulation (EC) No. 1272/2008. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf
Dossier Submitter's Response
Noted. Regarding the comments in the applicant's attached document, see comment 1.
RAC's response
Thank you, noted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	28
Comment received				
FR agrees with the classification proposal for environmental hazard and with the acute and chronic M factors.				
Dossier Submitter's Response				
Thank you!				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	29
Comment received				
Applicant agrees with the RMS conclusion for the Acute aquatic hazard evaluation and proposed classification. On the other hand, applicant acknowledges that, based on available experimental data, a steady state, whole fish wet weight lipid normalised and growth corrected BCF value of 813 was derived for proquinazid. This exceeds the BCF criteria of 500 for bioaccumulation according to CLP. However, A new irradiated water-sediment study has been conducted (Corteva study 220042, McLaughlin, 2023) to assess the degradation of proquinazid under sunlight conditions, as photolysis is an expected route of degradation. Initial findings have shown that the rate of degradation in water and sediment is significantly reduced under sunlight with DT50 in sediment approximate of 5 days and total system of <1 day. These new available rate of degradation may also have an impact on BCF values, as overall exposure may be significantly reduced then under realistic conditions. Final study report including confirmed values will be provided to add more information to the classification of Proquinazid in water and sediment as well as long term aquatic hazard classification and bioaccumulation classification. Applicant also generated 2 new aquatic organisms' studies which provides additional information (confirms and/or improves the current end points) for the classification evaluation for aquatic hazard. In this scope, applicant would like to present these 3 new study to for the consideration of RAC and RMS/EFSA upon request: • Mclaughlin, 2023, Irradiated Water-Sediment Study (Study ID: 220042) • Billa et al., 2022, PROQUINAZID: A PROLONGED SEDIMENT TOXICITY TEST WITH Lumbriculus variegatus USING SPIKED SEDIMENT (Study ID: 211160) • Gerke et al.,2021, PROQUINAZID: A SEMI-STATIC LIFE-CYCLE TOXICITY TEST WITH THE CLADOCERAN (Daphnia magna) (Study ID: 211087)				

Furthermore, the Applicant would like to provide detailed comments on the annexes of the CLH dossier in parallel with those submitted under Call for comments on the Renewal Assessment Report of Proquinazid (AIR IV) and relevant to the hazardous aquatic environment assessment, which also lists the new information generated and will be made available for RAC review, upon request. Due to the size and context this is being provided as an attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf
Dossier Submitter's Response
It is proposed that the new studies should be submitted by the applicant as Additional data and evaluated by the RMS in the revised RAR.
RAC's response
The three studies have been requested and assessed by RAC. The study by Mclaughlin (ID 220042; 2023) suggests that sunlight irradiation play a role in aerobic transformation of proquinazid in aquatic systems. Ultimate degradation, however, did not occur at levels > 70% in 28 days (or at a half-life < 16d), supporting the conclusion that the Substance is not rapidly degradable according to CLP criteria. Moreover, according to the specifications reported in the Guidance on the Application of the CLP Criteria (Ver. 5.0, July 2017; Annex III.5), the outcomes of degradation studies have no influence on BCF values used for assessing a substance potential for bioaccumulation. The study on *D. magna* performed by Gerke et al. (ID 211087; 2021) is scientifically well performed; validity criteria according to OECD 211 were fulfilled and reported data are considered reliable and relevant for classification purpose. The derived NOEC/E(I)C_{10} values are higher than those (proposed to be) used to derive the aquatic chronic toxicity classification for proquinazid. Therefore, the outcomes of this study do not affect the current classification proposal. For what concerns the study on *L. variegatus* by Billa et al. (ID 211160; 2022), RAC notes that the test was performed in line with GLP and that all validity criteria according to OECD 225 were fulfilled. Data obtained using spiked sediments are, however, not relevant for classification purpose as exposure via the water column is generally required.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	30
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 6-IODO-2-PROPOXY-3-PROPYLQUINAZOLIN-4(3H)-ONE;PROQUINAZID (ISO)

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	31
Comment received				
Applicant agrees with the RMS conclusion that "Since proquinazid is non-volatile and not included in Annex I or Annex II to II to Regulation (EC) 1005/2009 it can be concluded that it does not fulfil classification criteria for 'hazardous to the ozone layer'. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	France		MemberState	32
Comment received				
Was not reviewed.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United Kingdom	Corteva Agriscience International Sàrl	Company-Manufacturer	33
Comment received				
Applicant agrees with RMS conclusion for non-explosive Applicant agrees with RMS conclusion for not flammable. Applicant would like to note a potential typo on the UN Test method N2 which needs to be N1 Applicant agrees with RMS conclusion for not self-reactive Applicant agrees with RMS conclusion for not pyrophoric. Applicant agrees with RMS conclusion for not self-heating. Applicant agrees with RMS conclusion for no classification need for substances which in contact with water emit flammable gases Applicant agrees with RMS conclusion for not oxidising Applicant agrees with RMS conclusion for not corrosive ECHA note – An attachment was submitted with the comment above. Refer to public attachment Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf
Dossier Submitter's Response
Dossier Submitter acknowledges the typo regarding flammable properties. The test method referred to should be N1 and not N2.
RAC's response
Thank you, noted.

PUBLIC ATTACHMENTS
1. Redacted-CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf [Please refer to comment No. 1, 4, 7, 11, 13, 14, 18, 20, 22, 23, 27, 29, 31, 33]

CONFIDENTIAL ATTACHMENTS
1. CLH_Proquinazid_Corteva_Comments_HumanTox-Environmental_Feb2023.pdf [Please refer to comment No. 1, 4, 7, 11, 13, 14, 18, 20, 22, 23, 27, 29, 31, 33]