Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

3-chloro-4-(chloromethyl)-1-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one

EC Number: 262-661-3
CAS Number: 61213-25-0

CLH-O-0000001412-86-242/F

Adopted

30 November 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 3-CHLORO-4-(CHLOROMETHYL)-1-[3-(TRIFLUOROMETHYL)PHENYL]PYRROLIDIN-2-ONE

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: 3-chloro-4-(chloromethyl)-1-[3-(trifluoromethyl)phenyl]pyrrolidin-2-one
EC number: 262-661-3
CAS number: 61213-25-0
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2018	Germany		MemberState	1
Comment received				
The German CA agrees with the proposed classification. The estimated ATE of 500 mg/kg bw (p. 26) should be added to the proposal for inclusion in Annex VI.				
Dossier Submitter's Response				
Thanks for supporting the Spanish proposal of classification and labelling. According to CLP Regulation acute toxicity values are expressed as (approximate) LD_{50} (oral, dermal) or LC_{50} (inhalation) values or as acute toxicity estimates (ATE). When the available results are related to a range test, as it occurs for acute oral toxicity of Flurochloridone, appropriate conversion values included in Table 3.1.1 of CLP Regulation are used for ATE estimate. Since LD_{50} was observed to be in the interval of 300 mg/kg bw < LD_{50} (female rat) < 2000 mg/kg bw in Sieber study, classification as Acute Tox. 4 – H302: Harmful if swallowed was proposed and ATE of 500 mg/kg bw/day was established according to Table 3.1.1. Taking into account that the inclusion of substances in Annex VI does not cover the acute toxicity values (LD_{50}/LC_{50} or corresponding ATE) it does not seem appropriate to incorporate the ATE of 500 mg/kg bw/day for acute oral toxicity in the Flurochloridone inclusion.				
RAC's response				
Thank you for your comment, harmonised ATE value of 500 mg/kg bw will be added in Annex VI as requested in regulation (EU) 2017/776.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2018	Germany		MemberState	2

Comment received

The overall conclusion that Flurochloridone is devoid of a carcinogenic potential is agreed. However, with regard to the long-term study in mice (Sprague, 1985b), there are two points for which clarification might be useful. It should be confirmed that the increase in liver cell carcinoma in high dose males was not statistically significant. Furthermore, on page 53, an "increase in adrenocortical adenoma in males at all dose levels including controls" is mentioned. This claim is not substantiated by the figures in Table 24 because there was no dose response. What can be said is that, for unknown reasons, the general incidence of this finding, in all groups, was far above the mean historical control incidence. However, no range with regard to individual studies was reported.

Dossier Submitter's Response

Thanks for supporting the proposal of no classification for carcinogenicity

With respect to the clarifications requested with regard to the long-term study in mice (Sprague, 1985b), the Spanish CA would like to note the following points:

- The statistical analysis was made by comparisons of tumor incidence among groups using life table methods and Fisher´s exact probability or chi-square test. Differences were considered significant when $p < 0.05$. The administration of Flurochloridone did not produce a significant effect on any type of tumor. The increase in liver cell carcinoma in high dose males was not statistically significant.

- In the CLH Report, it is already mentioned that the higher incidence in adrenocortical adenomas observed in males at all dose levels including controls in comparation with historical control incidence were not dose dependent and without statistical significance. Its is also mentioned that this much higher incidence at all dose levels, including control group, in comparation with the historical control incidence was inexplicable.

- No range was reported in the historical control data for adrenocortical adenoma.

  The National Toxicology Program (NTP) historical control database (Haseman, 1984) provides the incidence of the more frequently-ocurring tumours in the NTP from 51 B6C3F1 mice studies until March 1983. The methodology used in this NTP publication considers that although there are situations in which the range may be helpful, there are problems associated with its use as a formal statistical analysis in the evaluation of tumor incidence data. The NTP philosophy is that after the comparison with the concurrent control, the most appropriate comparison is with the historical control rates rather than with historical control range, especially if they include a large number of studies.

RAC's response

Thank you for your comments and clarifications.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	France		MemberState	3
Comment received				
The proof of bone marrow exposure should be further substantiated (e.g.: based on available TK data) in order to totally exclude genotoxic potential in vivo.				
Dossier Submitter's Response				
In Silcock (2001a) and Silcock (2001b) toxicokinetic studies in rats after single doses (4 mg/kg bw and 200 mg/kg bw respectively), the residual radioactivity in tissues after 72 h was found in bone. On the other hand, in a chronic toxicity study in rats (Sprague, 1985a), statistically significant decreases in white blood cells (WBC) was registered from 40 ppm. It could be secondary to alterations in bone marrow. In conclusion, taking into account the available data, it could be concluded that flurochloridone can reach the bone marrow in rats.				
RAC's response				
Thank you for your comment and response. Although no proof of exposure was observed in the micronucleus studies, RAC agrees that the toxicokinetics studies gives some evidence that bone marrow could have been reached by flurochloridone. The decrease in WBC count in the chronic rat study may be of lower weight as the effect was reversible after 12 month, not dose-related, inside HCD and not associated with any histopathological changes in bone marrow.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	France		MemberState	4
Comment received				
Considering: - the severity of the reproductive effects observed in male rats (impact on fertility reproduction indexes) which is quite unusual. Indeed sperm count in rodents must be drastically reduced before an effect on fertility is seen. - the unknown underlying mechanism and the absence of data supporting non-human relevance - the low doses at which the effects are observed FR is of the opinion that classification Repr. Cat 1B for fertility may also be warranted in addition to Repr cat.1B for development.				
Dossier Submitter's Response				
Flurochloridone impaired fertility in male rats with testes and epididymides as the main targets. This was also supported by mechanistic data with a clear disturbance of the spermatogenic cycle. Regarding available information, the relevance in humans cannot be ruled out. Since category 1B according to CLP is required when based on data on animal studies a clear evidence of an adverse effect occurred, this category for fertility seems appropriate for flurochloridone. However, the clear and consistent evidence of reproductive toxicity in male rats was not observed in other species. In particular in fertility studies in rabbits (Wilcynski and Killinger, 1985c) and non-human primates (Wilcynski and Killinger, 1985d) and additionally in a sixth-month dietary study in dogs (Blair, 1983), in a 28-day dietary range finding study in mice (Oulette, 1982a) and in a 24-month dietary oncogenicity study in mice (Sprague, 1985b). The absence of effects in				

other studies suggested a potential specific sensitivity in rats and accordingly category 2 was proposed. However, the Spanish CA admits that category 1B could be considered if the consistency of data in other species is not deeemed sufficient to indicate a specific sensitivity in male rats.
RAC's response
Than you for your comment. RAC agrees that category 1B for fertility is appropriate for flurochloridone. Severe effects in rats have been observed and available data on the mode of action did not allow to exclude human relevance. Although no effects were observed in other species, RAC noted that dose levels used in some studies may not have been high enough to indicate that the other species may not be sensitive at all (e.g. monkeys, rabbits).

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2018	Germany		MemberState	5
Comment received				
In rats, the compound proved clearly toxic to male fertility. The study in monkeys is interpreted as an indication that this effect might be species-specific to the rat. However, it is difficult to compare a 12-week oral gavage study in rhesus monkeys with a 5 days/week dosing regimen to the continuous dietary treatment in the two-generation study in rats. Toxicokinetics may be different and duration of treatment in the monkeys might have been too short and group sizes too small. Usually, the rat is even considered a poor model of effects on spermatogenesis and male fertility since male rats are less sensitive than men. On balance, it is agreed that human relevance must not be excluded. These considerations would rather result in Category 1B than in Category 2 as proposed. However, since Category 1B has been proposed by the DS for developmental effects, the general conclusion (Repr1B, H360 Df) is supported.				
Dossier Submitter's Response				
The Spanish CA agrees that there is uncertainty in the comparison of the effects between rat and non-human primates primates (Wilcynski and Killinger, 1985d) considering the different study parameters. Indeed, it would have been more appropriate to have an intercomparison between species more accurate to confirm the specific sensitivity in rats. However, the absence of fertility effects were seen in other species besides non-human primates (see Comment 4). Accordingly, category 2 was proposed. However, the Spanish CA admits that category 1B could be considered if the consistency of data in other species is not deemed sufficient to indicate a specific sensitivity in male rats. It has been noted in the comment received that rat is a poor model of the effects on spermatogenesis and male fertility since male rats are less sensitive than men. However, this species is the preferred in the current validated studies for the assessment of the reproductive toxicity. Besides, the difference of sensitivity between rat and human does not rule out the possibility of an specific mechanism on fertility in male rats.				
RAC's response				
Than you for your comment. RAC agrees that comparative toxicokinetic data would have been needed to confirm a potential species specificity in rats. Overall, RAC considers classification as Repr. 1B appropriate for fertility effects induced by fluorochloridone.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
02.02.2018	Finland		MemberState	6
Comment received				
The lowest acute toxicity was ErC50 value of 0.0047 mg/l for algae (Scenedesmus subspicatus). For chronic toxicity all three trophic levels are not covered, as Smith (1990) fish study is not considered valid for classification purposes. Smith (1990) was conducted according to the OECD test guideline 204, which was deleted in 2014 by the OECD. Thus it is justified to not consider this study valid for classification purposes. The lowest chronic toxicity was NOErC value of 0,00028 mg/l for algae (Scenedesmus subspicatus). Valid chronic toxicity studies are missing for fish so according to the surrogate method flurochloridone should be assessed from the lowest acute toxicity value for fish (LC50 = 3.0 mg/l) and from the lowest chronic toxicity value for other trophic levels. On page 120 of the CLH proposal the lowest acute toxicity for algae is, however, used instead of the acute toxicity for fish. The lowest acute toxicity value for fish would result in the classification Aquatic Chronic 2, H411 instead of Aquatic Chronic 1, H410 as proposed on page 120 of the CLH proposal. However, as it is required to choose the most stringent classification in the surrogate method, this will not in the end change the classification as proposed by the dossier submitter. Based on classification criteria FI CA supports the proposed environmental classification Aquatic Acute 1, H400 with M-factor of 100 and Aquatic Chronic 1, H410 with M-factor of 100 for Flurochloridone.				
Dossier Submitter's Response				
The validity of the long-term toxicity test on fish was already included in the CLH proposal twice (points 11.6.1 and 11.7.2), stressing the unreliability of this result for the substance classification. We agree that the appropriate endpoint applying the surrogate method should be the acute toxicity LC50 for fish, instead the algae ErC50 included on 11.7.2 b). A correction in this paragraph b) is needed with a full justification, following your approach. Thank you. The final result would not change.				
RAC's response				
RAC agrees that the acute fish result should be used for the surrogate approach in this case, and that this does not affect the chronic classification.				

Date	Country	Organisation	Type of Organisation	Comment number
30.01.2018	France		MemberState	7
Comment received				
FR agrees with the classification and M factors (acute and chronic) proposals.				
Dossier Submitter's Response				
Thanks for your support.				
RAC's response				
RAC notes the comment and response.				

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Date	Country	Organisation	Type of Organisation	Comment number
26.01.2018	United Kingdom		MemberState	8
Comment received				
We note the endpoints from the key Lemna study are based on 14 days study duration. For consistency with hazard classification guidance, are 7-day endpoints available for the study?				
Dossier Submitter's Response				
We could not find that 7 days requirement you mentioned in the classification guidance. It would be helpful to state precisely where the guidance includes it. Nevertheless, in this Lemna study only 14-day endpoints were reported.				
RAC's response				
RAC notes that 7-day end points are not available in this case. The examples used in the CLP Guidance (e.g. see Section 4.1.3.4.1) cite 7-day end points for *Lemna*. OECD TG 221 (as well as the latest US EPA Guideline) also specifies a 7-day study duration. The CLP Guidance indicates that 7-day ErC50s are preferred for acute classification (section I.3.1). It does not explicitly discuss the preferred duration for the chronic end point for *Lemna*, but recognises that the study can be extended up to 14 days (v5, section I.2.3.2). Both 7- and 14-day endpoints have previously been used for chronic classification. RAC would welcome further clarification of this issue in a future guidance update. When a static test system is used, there is a risk of nutrient depletion over the 14 day time period, which could contribute to adverse effects. For this reason 7-day end points are usually preferred where available, and this also helps provide consistency in comparisons between chemicals. However, as a semi-static exposure regime was used for this substance, nutrient depletion would probably not have been a problem and so RAC considers it unlikely that 7-d end points would affect the classification in this case.				

Date	Country	Organisation	Type of Organisation	Comment number
02.02.2018	Belgium		MemberState	9
Comment received				
Based on the data available in the CLH report, BE CA supports the proposed environmental classification with Aquatic Acute 1, H400 (Macute=100) and Aquatic Chronic 1, H410 (Mchronic =100). We agree that no valid chronic studies for fish are available and that the surrogate approach is of application. Although not affecting the final conclusion on the classification we are of the opinion that the reasoning behind the surrogate approach (based on the LC50) for flurochloridone is not correct. The acute toxicity data for the surrogate approach to look at are those for the other trophic levels for which no adequate chronic data are available. Reliable chronic data are available for invertebrates, algae and aquatic plants. In this case acute toxicity data for fish should thus be considered. Based on the LC50 fish (between 1 and 10 mg/L) and the fact that the substance is not rapidly degradable a classification Aquatic Chronic 2, H411 is warranted. However according to the most stringent outcome from both NOEC and LC50, the substance warrants classification with Aquatic Chronic 1, H410 (M=100) based on the chronic data on algae (Scenedesmus subspicatus with 72hNOErC= 0.28µg/L).				

Dossier Submitter's Response
We agree that the appropriate endpoint applying the surrogate method should be the acute toxicity LC50 for fish, instead the algae ErC50 included on 11.7.2 b). A correction in this paragraph b) is needed with a full justification, following your approach. Thank you. The final result would not change.
RAC's response
RAC agrees that the acute fish result should be used for the surrogate approach in this case, and that this does not affect the chronic classification.