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-methylpyrazole

EC Number: 215-925-7
CAS Number: 1453-58-3

CLH-O-0000006718-63-01/F

Adopted

5 December 2019

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-methylpyrazole
EC number: 215-925-7
CAS number: 1453-58-3
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2019	Germany		MemberState	1
Comment received				
The German agrees with the proposed harmonised classification of 3-methylpyrazole as - Repr 1B, H360D - Acute Tox 4, H302 - Eye Dam 1, H318 - STOT RE 1, H372 (lung) With regard to Skin Corrosivity a classification as Skin Corr 1, H314 without a subcategory is considered appropriate (see below).				
Dossier Submitter's Response				
Thank you for your comment and support				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	2
Comment received				
The SE CA agrees with the proposed classification of 3-methylpyrazole as Repr. 1B, H60D based on clear evidence of increased incidences of severe malformations in the urogenital tract in three rat prenatal developmental studies at dose levels where there were no marked maternal toxicity.				
Dossier Submitter's Response				
Thank you for your comment and support				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2019	Germany		MemberState	3
Comment received				
A guideline compliant prenatal developmental toxicity study (OECD TG 414) clearly showed teratogenic effects in the absence of considerable maternal toxicity. At the high dose (90 mg/kg bw) the maternal body weight was slightly, but significantly lower than control values at GD15 and GD20 (-5.5 %). Therefore, the maternal NOAEL was 45 mg/kg bw (at lower food consumption ≥ 45 mg/kg bw/d). The pups showed severe soft tissue malformations (agenesis of kidney(s) and ureter, displacement of aortic arch and dilation of efferent urinary tract) in absence of considerable maternal toxicity. Although these severe effects were observed only in the highest dose group, they could not be explained with the slight reduction of the maternal body weight. Beside these malformations, the thoracic vertebral bodies were also altered. These skeletal alterations were classified as variation. Furthermore, the body weight of the pups was significantly reduced in the two highest dose groups. Based on the decreased body weight, the NOAEL (fetal) was 15 mg/kg bw. In addition, two further non guideline compliant studies produced the same urogenital effects at doses without maternal toxicity. The authors consistently described severe urogenital malformations and reduced body weights of the pups. The interpretation of these effects as substance-related effects is supported by the fact that toxicokinetic data obtained in an in vivo study showed that 3-methylpyrazole crosses the placental barrier (see Anonymous 11 (1982)). Taken together, the proposed harmonised classification Repr. 1B, H360D, is clearly justified.				
Dossier Submitter's Response				
Thank you for your comment and support				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2019	Germany	SKW Stickstoffwerke Piesteritz GmbH	Company-Importer	4
Comment received				
SKW Stickstoffwerke Piesteritz GmbH does not agree with the proposed classification of 3-Methylpyrazole for Reproductive Toxicity (Repr. 1B, H360D) as contained in the Annex VI Report submitted by BCA. The available data base does not allow for unanimous classification of 3-Methylpyrazole into category Repr. 1B as has been proposed in the CLH report of BCA, actually without an extended discussion of the contradictory results and the various shortcomings of the reviewed studies. On the other hand, are there indications for a substance specific teratogenic effect of 3-Methylpyrazole which would make it difficult to clearly substantiate a classification into category Repr. 2 only. Considering respective study results gained from two closely related substances (i.e. Pyrazole and 3,5-Dimethylpyrazole) category Repr. 2 seems be more appropriate. Taking into account this unsatisfactory situation for the registrant, it seems to be a valid option, to execute of a well-conducted, and possibly extended, OECD 414 study by a study design aiming for discrimination between in particular maternal and teratogenic				

effects. Therefore, a developmental study in rodents by oral route of exposure is proposed by the registrant to clarify the uncertainties described above. Detailed comments are provided as a separate document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Methylpyrazol_assessment develop. tox.pdf
Dossier Submitter's Response
Thank you for your comment. However, BECA still considers a classification as Repr. 1B H360D appropriate regarding the severe fetal malformations observed in the urogenital tract and/or in the cardiovascular system. Our evaluation was carried out on the basis of the available studies (full study report and/or information in the registration dossier). Concerning the 2 studies not mentioned in the registration dossier, BECA is unable to take position only based on the short summary provided during the public consultation. Nevertheless, the available positive results that are considered adequate for classification should not be overruled by negative findings. BECA would like to emphasize that severe malformations (agenesie of kidney(s), agenesie of ureter(s) and malpositioned aortic arch) (Devtox.org) were observed in the absence of considerable maternal effects.
RAC's response
Thank you for additional information regarding the developmental toxicity of 3-methylpyrazole. RAC will consider the new studies in the assessment.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2019	Germany		MemberState	5
Comment received				
Based on the data provided by the DS, the harmonised classification as Acute Tox. 4, H302 is justified. Data obtained by guideline compliant testing yielded a LD50 value between 300 and 2,000 mg/kg bw. The conversion of the dose range into a converted ATE value of 500 mg/kg bw is warranted.				
Dossier Submitter's Response				
Thank you for your comment and support				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2019	Germany		MemberState	6
Comment received				
In chapter 10.4.3 it is concluded that Skin Corr. 1 is appropriate based on the results of an in vitro test (OECD TG 431, EpiDerm). It is stated in the Guidance on the application of the CLP criteria (2017) on page 273 that the test cannot discriminate between the categories 1B and 1C. In addition it reads on page 280 "In particular OECD TG 431 concludes that some results fall in the category 1B/1C. Category 1B/1C is not an option in CLP. However, a WoE assessment may lead to a conclusion about the subcategory but if this is not the case, category 1 should be assigned." Such a WoE assessment is not available in the CLH-report. Thus, based on the given information Skin Corr. 1, H314 is				

appropriate as the results of the EpiDerm-Test do not allow the discrimination between categories 1B or 1C.
Dossier Submitter's Response
Thank you for your comment and support
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2019	Germany		MemberState	7
Comment received				
Based on the available data, the harmonised classification Eye Dam. 1, H318 is justified.				
Dossier Submitter's Response				
Thank you for your comment and support				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2019	Germany		MemberState	8
Comment received				
Based on the available results obtained in mice, there were adverse and irreversible alterations in the lung (Clara cells) which deserve a STOT RE-classification. Clara cells contain high amounts of cytochrome P450 enzymes. The primary secretory product is blastokinin or in humans CC16. Beside this protein, the cells secrete many essential substances, including KL-6 protein and further glycoproteins, lipids and proteins providing chemical and physical protection for both pulmonary surfactant and small airways. The mentioned cells have a fundamental function in the biotransformation of xenobiotics in the lungs. Therefore, Clara cells play an important function in protecting the airways from the harmful influence of toxic substances. Furthermore, it is believed that progenitor Clara cells participate in the repair of airway epithelial damage (Rokicki et al., 2016). Therefore, the adverse alterations of the Clara cells observed in mice are of relevance for human health. The reasoning for the STOT RE 1 proposal in table 35 and chapter 10.12.2 is confusing, because all mentioned doses seem to justify STOT RE 2 and not STOT RE 1. Some further arguments should be considered in addition. Based on the results of the key 90-day study conducted by Anonymous 24 (2000), the incidence and severity of Clara cell alteration as a consequence of prolonged oral dosing is clearly dose-dependent and irreversible. The adverse effects on Clara cells were observed from 10 mg/kg bw/d onwards. At 10 mg/kg bw/d, the border between STOT RE 1 and STOT RE 2, the effects were grade 1 and 2, however did not reverse within a subsequent recovery period of 4 weeks. Thus STOT RE 1, H372 (lung) should be considered. Moderate to severe Clara cell alterations were also seen in two 28 d studies in mice at 70 mg/kg bw/d and 154 mg/kg bw/d, respectively. The observation that the incidence was already 100 % at 300 ppm (70 mg/kg bw/d for males (corresponding to about 23 mg/kg in a 90-day design) and no lower dose was tested is considered as supportive for STOT RE 1.				

Dossier Submitter's Response
Thank you for your comment and your support regarding classification for STOT RE in category 1. BECA recognize that the reasoning in table 35 and chapter 10.12.2 is confusing. As you mentioned in your comment, based on the effect observed in lung at a borderline dose (10 mg/kg bw/d) in one study and the irreversibility of this effect, BECA considers a classification as STOT RE cat. 1 appropriate.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2019	Netherlands		MemberState	9
Comment received				
Several repeated dose toxicity studies were presented. Three studies with mice (B6C3F1) that were guideline (TG407 or 408) and GLP compliant, indicate adverse effects on the lungs. The effects included hypotrophy (focal and diffuse), clara cell lesions/alterations combined with lung weight changes indicating adverse changes to lung function. The effects were considered to be treatment related. In line with the CLP criteria for effects warranting classification (EC 1272/2008, Annex I, paragraph 3.9.2.7.3) these effects can be considered as: 'significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination' The other studies (1x mouse and 3x rat) do not indicate such effects. In the mouse study (non-guideline and non-GLP), a limited number (3) of animals were used in each group. Furthermore, the doses used were too low. Two out of three rat studies did not follow a guideline and were not GLP compliant. The dosing in the single rat study that was guideline compliant was too low. Therefore, these studies cannot contradict the effects in lungs in the guideline compliant studies with mice. On basis of the effects in lungs, the DS proposed classification of 3-methylpyrazole as STOT RE 1. However, the NL-CA notes that the effects on the lungs were observed at effective dose levels between 30-300 mg/kg bw/day in the two 28-day studies with mice and between 10-100 mg/kg bw/day in the 90-day study with mice. Effects at these dose levels warrant classification for STOT RE 2, not 1 according to the CLP criteria (EC 1272/2008, Table 3.9.3 and section 3.9.2.9.5). Overall the NL-CA agrees with classification as STOT-RE, but category 2, not 1.				
Dossier Submitter's Response				
Thank you for your comment. BECA recognize that the reasoning in table 35 and chapter 10.12.2 is confusing. In the subchronic toxicity study (anonymous 24, 2000), a dose related increased incidence of Clara cell alteration was observed. This effect was already observed, at 10 mg/kg bw/d (in 7 males out of 10 and 4 females out of 10). In this study, 10 animals/sex/group were observed 4weeks after the exposure period. Clara cell alteration was again observed after this recovery period and was considered irreversible Furthermore, in the short term toxicity study (anonymous 20, 1997), histopathological changes in lung were already observed at the lowest dose (corresponding to 70/82 mg/kg bw/d in males/females). These effects (Clara cell alteration and proliferation of grade 2 and 3) did not reverse within a 4weeks recovery period and are thus considered irreversible.				

Based on the effect observed in lung at a borderline dose (10 mg/kg bw/d) in one study and the irreversibility of this effect, BECA still considers a classification as STOT RE cat. 1 appropriate.
RAC's response
Noted.

PUBLIC ATTACHMENTS
1. Methylpyrazol_assessment develop. tox.pdf [Please refer to comment No. 4]