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: 3,5-dimethylpyrazole
CAS number: 67-51-6
EC number: 200-657-5
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	1
Comment received				
The DE CA would like to thank the Belgian CA for assessing the toxicity of 3,5-dimethylpyrazole and supports the CLH proposal. The available data and information are described in detail and are sufficient for a conclusive decision on the assessed endpoints.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Sweden		MemberState	2
Comment received				
We thank the Belgian CA for the proposal for harmonised classification of 3,5-dimethylpyrazole. We notice that there is no information on the toxicokinetics of the substance included in the CLH-proposal. A short description of the ADME can be valuable in the evaluation of the toxicity. In this case, it would be especially informative with information about potential metabolites, since the Belgian CA proposes three different CLH proposals for similar substances (i.e. 3,5-dimethylpyrazole, 3,4-dimethyl-1H-pyrazole and 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate).				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Germany	<confidential>	Company-Manufacturer	3
Comment received				
RAC please consider below comments for your classification opinion. Especially the possibility of a secondary response should be relfected in the category for the reproductive toxicty endpoint.				
Dossier Submitter's Response				
RAC's response				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Netherlands		MemberState	4
Comment received				
DS concludes classification as Repr. 1B (H360FD) is warranted based on a disturbance in the male reproductive system and pup mortality/malformations. Concerning adverse effects on fertility and sexual function: - In a EOGRT study with DNT and DIT cohorts a lower prostate weight was found at the highest tested dose (100 mg/kg bw/d) for F0 males. In addition, a lower seminal vesicle weight was found at the highest tested dose in F0, C1A and C1B males. Microscopic findings in the prostate and seminal vesicles were found at the highest dose for F0 and C1A males and include decreased glandular secretions and an overall reduction in glandular size. None of the male reproduction parameters (including fertility index) were significantly or dose-related affected. - P.11. In the summary table of the EGORT it is noted "Male reproductive parameters: sperm count decreased." However, on page 17, it is stated that "Male reproduction parameters were examined and did not reveal significant change. Sperm count (epididymis) showed a reduce but this modification was not dose-related (768.2, 707.0, 736.3 and 716.5 Mio/g, resp. at 0, 20, 50 and 100 mg/kg bw/d)". - In a GLP combined repeated dose toxicity study, with reproduction and developmental toxicity screening test, microscopic modifications in the epididymides and testes were found in male rats at the highest tested dose (200 mg/kg bw/d). These include oligospermia (1/6), seminiferous cell debris (3/6), degeneration/depletion of spermatocytes (6/6) and an increase in spermatic giant cells (5/6). However, no information is available on microscopic modifications in control or lower dose groups (p. 28). - P. 28. A lower fertility index (60% vs 80% in control) and conception index (66.7% vs 80% in control) was observed in the combined study, however no information on statistics was available to DS (8/2 in control group vs 6/3 in the high dose group). This information is not included in the conclusion for fertility effects on p. 30. In the table on p.29 only the fertility index for the control and the highest dose are included, with "no info" for the low and mid doses. However, in the registration dossier it is stated that the 20 mg/kg bw/d and 60 mg/kg bw/d dose groups both have 90% fertility index, as well as conception index of 90%. - Overall, there are some indications for adverse effects though some uncertainties are noted. If observed fertility effects are statistically significant, NL-CA would agree that classification as Repr. 1B for fertility is warranted. However, in absence of statistics information, NL-CA argues classification as Repr. 2 for fertility could be more appropriate based on disturbances observed in the male reproductive system.				

Concerning adverse effects on development: - DS concludes Repr. 1B is warranted based on higher pup mortality in the EOGRT and combined toxicity study and an increased incidence of malformations and variations observed in the prenatal developmental toxicity study which cannot be attributed to maternal toxicity. NL-CA agrees with this conclusion. NL-CA further agrees with the 'no classification' for adverse effects on/via lactation. It is noted that the DS has proposed a classification of Repr. 1B (H360DF) for 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate (CAS 202842-98-6). Did the DS explore whether a read-across method would apply?
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	5
Comment received				
Regarding fertility, the EOGRTS demonstrates effects on fertility, with a proposal for a Repr.1B classification. FR is in agreement with the DS that the doses in the EOGRTS are too low (20, 50 and 100 mg/kg bw/day): in the light of the results of the overall toxicological dataset with 3,5-dimethylpyrazole in addition with the results of the EOGRTS, FR considers that the EOGRTS should have been performed with higher doses. To support this argument, did the DS have access to the DRF study? However, the second available study, the combined repeated dose toxicity study have been performed with higher top dose (200 mg/kg bw/day). In this study, the fertility index was reduced and histopathological changes were observed in several male reproductive organs. A Repr. 1B classification is warranted in view of these greater effects at higher doses. FR supports category Repr. 1B for fertility. Regarding developmental effects some malformations were observed : external finding with Polydactyly » Supernumerary – Digit in 3 fetuses in 2 litters (at the top dose) and skeletal findings with short humerus (malformations) and bent scapula blade (grey zone) were observed in different litters at the top dose also. There are no dose-related observations. There were also some variations observed at the top dose (umbilical artery variation, sutural bones, abnormal pelvic gridle alignment, additional ossification site on the sternebra, incomplete ossification on vertebra and on metatarsal). Moreover, there were effects on pups mortality in both studies. To conclude, FR supports category Repr. 1B for development.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Sweden		MemberState	6
Comment received				

Fertility
The Swedish CA supports the proposed classification as Repr. 1B for effects on fertility based on the information presented in the dossier. There is clear evidence of effects on male reproductive organs: adverse histopathological findings in male reproductive organs and decreased male reproductive organ weights at 200 mg/kg bw/d in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, and decreased male reproductive organ weights at 100 mg/kg bw/d in the EOGRTS. We also note that the highest dose in the EOGRTS (100 mg/kg bw/d) is lower than the highest dose (200 mg/kg bw/d) in the combined study, and that there was no adverse general toxicity in the parental generation at this dose. Thus, it is possible that more pronounced effects could have been observed at a higher dose level in the EOGRTS, including histopathological changes in male reproductive organs.

Developmental toxicity
The Swedish CA largely agrees that the information presented in the dossier points towards the proposed classification as Repr. 1B for effects on development, based on the increased incidence of fetuses with malformations and variations in the highest dose group (200 mg/kg bw/d) in the PNDT study. However, it is difficult to draw a firm conclusion based on the information presented in the dossier, which lacks details about the malformations, such as a clear description of the types and numbers of malformations, historical control data and the incidence of malformations in the low and mid dose groups.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	7

Comment received

The DE CA supports the proposed classification of 3,5-dimethylpyrazole as Repr. 1B for fertility based on the following effects: male reproductive organs were affected by exposure to the test substance and histopathological effects such as oligospermia, presence of seminiferous cell debris and degeneration/depletion of spermatocytes (up to a massive degree) were observed.
The DE CA supports the proposed classification of 3,5-dimethylpyrazole as Repr. 1B for development based on the following effects: pup mortality, and malformations/variations. It is assumed that maternal systemic toxicity cannot explain the observed developmental effects.
It was noted that there are uncertainties regarding the historical control data (HCD) for the incidence of variations (Table 39). No information is available e.g. on time range, laboratories, and species.
The classification proposal is based on two reliable oral GLP studies performed with the substance in rats (Wistar) according to OECD TG 422 and to OECD TG 443.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment

				number
13.10.2023	Germany	<confidential>	Company-Manufacturer	8

Comment received

Developmental toxicity:
In a developmental toxicity study (OECD 414) with rats, three doses of 3,5-DMP were orally applied (20, 60 and 200 mg/kg b.w.). Details on the study design and effects of minor relevance are discussed in the submission of the Lead registrant LANXESS. The conclusions are fully supported but not repeated below one by one.
Relevant treatment-related effects on development of rats were only seen at the highest dose without dose response relationship. Polydactyly was observed in three pubs of two litters, but no such findings were observed at the same dose in the screening study (OECD 422) or at 100 mg/kg b.w. in the extended one generation study (OECD 443). This reduces the regulatory weight of this finding. Additionally bent scapula was observed in 6 fetuses from 3 litters versus 4 fetuses from 4 litters in the control group. This slight increase which is also focused on certain litters is likely a consequence of the chondrodystrophy syndrome known for this rat strain and should not be seen as critical malformation relevant for classification. It is known to resolve postnatally. The same is true for the observed short humerus and observed variations. (Mitchard and Stewart 2014)
Generally, it may be concluded that observed dosing related effects with generally low incidence in the high dose group are secondary to systemic effects caused by 3,5-DMP. In this context it must be kept in mind that systemic effects were observed at this dose level and below and have triggered classification as STOT RE 2. Precautionary classification for developmental toxicity in category 2 may be warranted to reflect the observations but there is no indication for a higher level classification, i.e. category 1B.

Mitchard, T. and J. Stewart (2014). "Reduced post-natal versus pre-natal incidence of bent long bones and scapulae in a preliminary investigation using the Han Wistar rat." Reprod Toxicol 45: 39-44.

Reproductive toxicity:
In an extended-one-generation study (OECD 443) with rats, three doses of 3,5-DMP were orally applied (20, 50 and 100 mg/kg b.w.). Further details on the study design are discussed in the review of the lead registrant LANXESS. No adverse effects on mating performance, fertility, fecundity, gestation, partition, or lactation were identified. No test article related immunotoxicity or neurotoxicity effects were evident. No changes in sperm count, sperm mobility, velocity, or morphology were noted following 3,5-DMP administration in the cohort 1A. Some minor effects at the mid and high dose on F0 pup body weight and marginally higher number of pup mortality in F0 generation litters (HD) as well as increased incidence of offspring mortality for the F1 generation (HD) were observed. These common and unspecific effects are not considered relevant for category 1B, especially in case it must be expected that these are secondary to general systemic effects as clearly observed in the 90-day study at this dose level (STOT RE classification!). Similarly, the 20% weight reduction in prostate may be adverse and could be considered for precautionary category 2 classification but without any other hormone sensitive organ change and in the absence of effects on the male reproductive performance this does not justify classification in category 1B.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment

				number
13.10.2023	United Kingdom	Health and Safety Executive	National Authority	9
Comment received				
3,5-dimethylpyrazole: Hazard class: Reproductive Toxicity Sexual function and fertility 'We would welcome further discussion on whether 3,5-dimethylpyrazole shows a 'clear' adverse effect on sexual function and fertility. The combined repeated dose toxicity study with the reproductive/developmental screening study indicates some testicular toxicity and infertility at the top dose (200 mg/kg bw/d). The conception index at the top dose is 66.7%, which differs by 1 non-pregnant female compared to the control (80%). Is this a clear adverse effect on sexual function and fertility?' Developmental toxicity 'Could the DS please provide HCD for the malformations observed in the prenatal developmental toxicity study, if available. In addition, the effect 'bent scapula' is regarded as a variation by 'ECETOC' and a grey zone in 'DevTox', due to it being a transient finding. Can the DS/RAC clarify their position on this finding?'				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	United Kingdom	LANXESS	Company-Manufacturer	10
Comment received				
Following a review by an independent external developmental and reproductive toxicology (DART) expert, we dispute the proposed reproductive toxicant category 1B classification. It is our understanding that the DART studies support the existing reproductive toxicant category 2 classification and detailed comments and analysis to support this are provided in the attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment_3,5-Dimethyl pyrazole_LXS_Public.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Comment_3,5-Dimethyl pyrazole_LXS_Confidential.pdf				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	11
Comment received				

The classification Acute Tox. 4, H302 is supported by FR.
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	12
Comment received				
The DE CA supports the proposed classification of 3,5-dimethylpyrazole as Acute Tox. 4 (H302) and the derived ATE value of 1717 mg/kg bw. The classification proposal is based on a reliable oral study performed with the substance in SD rats according to OECD TG 401 and GLP.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Germany	<confidential>	Company-Manufacturer	13
Comment received				
Acute Tox 4 agreed.				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	14
Comment received				
The classification STOT RE 2, H373 is supported by FR.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	15
Comment received				
The DE CA supports the proposed classification of 3,5-dimethylpyrazole as STOT RE 2 (H373) (liver) based on the following effects: changes in liver weights together with changed parameters of organ dysfunction, such as centrilobular degeneration/regeneration of hepatocytes, significant increases in AST and ALT, hepatocellular basophilia and				

apoptosis/single cell necrosis with severity as "up to marked", and hepatocellular karyomegaly. In the registration dossier, it is concluded that "males at this dose level (60 mg/kg bw/d) had toxicologically relevant liver findings at the microscopic examination." The classification proposal is based on two reliable oral GLP studies performed with the substance in rats (Wistar) according to OECD TG 422 and to OECD TG 443. The DE CA supports the proposed classification of 3,5-dimethylpyrazole as STOT RE 2 (H373) (blood) based on signs of anaemia (e.g. effects on the parameters Plt, PT, APTS, MCV, MCH, RBC). Furthermore, spleen was also affected (increased incidence of splenic pigment), which supports that the test substance affects the haematological system. The classification proposal is based on a reliable oral GLP study performed with the substance in rats (Wistar) according to OECD TG 443.
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Germany	<confidential>	Company-Manufacturer	16
Comment received				
STOT RE category 2 agreed.				
Dossier Submitter's Response				
RAC's response				

PUBLIC ATTACHMENTS
1. Comment_3,5-Dimethyl pyrazole_LXS_Public.pdf [Please refer to comment No. 10]

CONFIDENTIAL ATTACHMENTS
1. Comment_3,5-Dimethyl pyrazole_LXS_Confidential.pdf [Please refer to comment No. 10]