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: 3,4-dimethyl-1H-pyrazole
CAS number: 2820-37-3
EC number: 429-130-1
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	1
Comment received				
Saturation of excretion is a crucial point that must be taken into account when examining toxicity after repeated dosing because excretion is a key detoxification process. Excretion is saturated at 30 mg/kg bw/d and above in rats. Toxic effects from DMP exposure manifest at doses where internal kinetics are non-linear, resulting in internal exposures above dose proportionality. A detailed description of DMP kinetics has been provided in pages 1-8 of the attached comments. Hazardous properties observed under the excretion-saturated conditions are of doubtful relevance to human health hazard assessment. In this regard, it should be further noted that human to rat comparison of Organic Anion Transporters involved in excretion suggests that human excretion would be more effective than rat (pages 5-6), increasing questionable relevance to human health hazard assessment. Additionally, recently conducted studies for environmental hazards were not evaluated by the DS (see pages 25-26). This new data clearly shows that the current legal classification (Aquatic Chronic 3, H412) is not necessary and should be removed since the lowest chronic effect value is greater than 1mg/L and for non-rapidly biodegradable substances there are only classification categories 1 and 2 available with the respective thresholds of less than or equal to 0.1 mg/L and less than or equal to 1 mg/L. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMP_CLH_comments_BASF SE.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment

				number
13.10.2023	Belgium	Cefic - Fertilisers Efficiency Enhancers	Industry or trade association	2
Comment received				
We would like to bring ECHA's attention to the need of assessing 3,4-DMP based on a robust weight of evidence methodology. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Fertilisers Efficiency Enhancers comments on the CLH proposal for 3 4 DMP.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Sweden		MemberState	3
Comment received				
We thank the Belgian CA for the proposal for harmonised classification of 3,4-dimethyl-1H-pyrazole. 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). Furthermore, in the ARN for pyrazoles (ECHA 2021) ECHA proposed to apply read-across from 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate (EC 424-640-9) to 3,4-dimethyl-1H-pyrazole. Was this considered by the dossier submitter to be used as supporting evidence in the weight of evidence assessment?				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	4
Comment received				
The DE CA would like to thank the Belgian CA for assessing the toxicity of 3,4-dimethyl-1H-pyrazole and supports the CLH proposal. The available data and information are reported in detail and are sufficient for a conclusive decision on the assessed endpoints. The substance with EC no. 429-130-1 is named "3,4-dimethyl-1H-pyrazole" in the CLH report and "4,5-dimethyl-1H-pyrazole" on the ECHA dissemination site. The chemical name should be clarified/discussed under substance ID. The substance is solid. However, the viscosity was determined utilizing a capillary viscosimeter according to a test procedure for liquids. Therefore, we wonder if the viscosity was determined for a solution or at elevated temperatures when the substance is molten. Could you please add more information on the temperature and/or solution concentration (if the viscosity was determined for a solution)? If you don't have further information, we suggest to remove this value from the dossier as it is confusing to us.				

Dossier Submitter's Response
RAC's response

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	5
Comment received				
The harmonised classification proposal considers carcinogenicity data from rats but has not included available information on carcinogenicity in mice. This may result in an incomplete picture of the carcinogenic hazard potential of 3,4-DMP. A key finding was absence of neoplastic effects in mice exposed up to 98.6 mg/kg bw/d and is summarized on pages 9-10 of the attached comments. In rats, tumor formation was observed only at a dose exceeding the maximum tolerated dose. The genotoxicity studies conducted with 3,4-DMP were negative, suggesting a non-mutagenic mode of action for tumor formation. Carcinogenic effects in rats were only observed at doses compromising detoxification processes and are unlikely to be human relevant (discussed in pages 10-14). ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMP_CLH_comments_BASF SE.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	6
Comment received				
The carcinogenic effect at the higher dose level was associated with decreased body weight (-12%) and high morbidity (44%). Could you please add information in the table 16 on confounding effect by excessive toxicity and discuss it in the section comparison with the CLP criteria? There was 22 males found dead or sacrificed moribund during the study. It is indicated regarding males with nasal tumors, p22 "Moreover, 5 males out of these 7 affected males died prematurely". Do you have information on the reasons for the death of the other animals, and at what time in the study did they die? Even though, information is lacking regarding mortality, the potential carcinogenic effect of the 3,4-dimethyl-1H-pyrazole should not be ignored. FR supports category Carc. 2 for carcinogenicity.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Belgium	Cefic - Fertilisers	Industry or trade	7

		Efficiency Enhancers	association	

Comment received

The Dossier Submitter assessed one animal study (combined chronic toxicity/carcinogenicity study, page 12 to 13 of the Annex XV dossier) to conclude that the classification carcinogenicity category 2 is warranted. In this regard, we would like to quote the ECHA Guidance document on Information Requirements and Chemical Safety Assessment R7a (2017) (hereinafter 'ECHA Guidance' in this document):

"With respect to carcinogenic potential and potency the most appropriate source of information is directly from human epidemiology studies (e.g. cohort, case control studies). In the absence of human data, animal carcinogenicity tests may be used to differentiate carcinogens from non-carcinogens. However, the results of these studies subsequently have to be extrapolated to humans, both in qualitative as well as quantitative terms. This introduces uncertainty, both with regard to potency for as well as relevance to humans, due to species specific factors such as differences in chemical metabolism and toxicokinetics and difficulties inherent in extrapolating from the high doses used in animal bioassays to those normally experienced by humans".

Moreover, according to the CLP Regulation (Regulation (EC) No 1272/2008), classification for a substance as a carcinogen is a process that involves two interrelated determinations: evaluation of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories (see 3.6.2.2.2).

In our opinion, the classification proposal by the Dossier Submitter does not meet the criteria described above since it considers carcinogenicity data limited to a single experiment, leaves questions regarding the adequacy of the design, conduct and interpretation of studies unresolved, and the severity of the effects observed is limited.

In rats, tumour formation was observed only at a dose exceeding the maximum tolerated dose and at doses compromising detoxification process. For this reason they are unlikely to be human relevant.

Therefore, available data justify that 3,4- DMP does not warrant a classification for carcinogenicity. A Carcinogenicity Cat 2. classification could be considered only based on the precautionary principle and worst-case scenario.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Fertilisers Efficiency Enhancers comments on the CLH proposal for 3 4 DMP.pdf

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	8

Comment received

The significantly increased incidence of malignant epithelial tumours in the posterior part of the nasal cavity, which was observed in males, clearly and conclusively warrants a classification as Carc. 2.

Dossier Submitter's Response

RAC's response

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Netherlands		MemberState	9
Comment received				
DS concludes classification as Repr. 2 H361f is warranted based on alteration of the female and male reproductive system. - P.33. Significant changes were observed in reproductive organ weight (uterus, ovary, prostate) and histopathology in both female and males and observed in several studies (2 generation reproduction tox; 90 day repeated toxicity; 28 day repeated toxicity) and species (rat, mouse, dogs). Overall, it is agreed that these effects are considered not to be secondary to other toxic effects. However, these are considered not to present clear evidence for adverse effects on fertility and sexual function. - No significant dose-related effects on fertility parameters were found in the 2 generation rat study, as stated on p. 31: "However, in the F0 generation, fertility index tended to decrease at the highest dose, even if the change was not dose-related.". However, it is noted that the highest dose in the 2-generation rat study is low, as no general toxicity was observed. - Overall, there are some indications for adverse effects though some uncertainties are noted. Based on the available studies with 3,4-dimethyl-1H-pyrazole, NL-CA agrees with the proposed classification. DS concludes classification based on developmental effects is not warranted as the mean number of live pups was unaffected and no malformations were observed in the available studies with 3,4-dimethyl-1H-pyrazole. NL-CA agrees. 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 structurally similar compounds, i.e. 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate (CAS 202842-98-6). Did the DS consider a read-across method?				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Belgium	Cefic - Fertilisers Efficiency Enhancers	Industry or trade association	10
Comment received				
A robust weight of evidence assessment of all available data should be performed in the assessment of 3,4-DMP for reproductive toxicity. A two-generation reproduction toxicity study according to OECD 416 guidelines				

(Anonymous, 2021 – page 19 of the Dossier) shows lack of adverse effects on sexual function and fertility. Moreover, the available mechanistic data suggests that detoxification via excretion by the kidneys is more efficient in humans compared to rats, making humans less prone to the toxic effects of the substances.

When considering whether the effects observed in studies regarding the substance are adverse or not, we would like to quote the ECHA Guidance:

"Although not required by REACH, toxicokinetic studies may be helpful in the evaluation and interpretation of repeated dose toxicity data, for example in relation to accumulation of a substance or its metabolites in certain tissues or organs as well as in relation to mechanistic aspects of repeated dose toxicity and species differences. Toxicokinetic information can also be used in the selection of the dose levels. When conducting repeated dose toxicity studies it is necessary to ensure that the observed treatment-related toxicity is not associated with the administration of excessive high doses causing saturation of absorption and detoxification mechanisms. The results obtained from studies using excessive doses causing saturation of metabolism are often of limited value in defining the risk posed at more relevant and realistic exposure levels where a substance can be readily metabolised and cleared from the body. It is suggested that a key element in designing better repeated dose toxicity studies is to select appropriate dose levels based on results from useful metabolic and toxicokinetic investigations".

In fact, due to compromised detoxification processes in the reproductive toxicity studies, the resulting internal exposure becomes irrelevant to human hazard assessment because effects occur only under experimental conditions where detoxification by excretion is impaired. Therefore, the observed effects at high doses are disproportionate and do not reflect human hazard potential.

Therefore, based on available data and on a weight of evidence approach, we propose that classification Repro Cat 2 for fertility and for reproductive toxicity as such not be warranted.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Fertilisers Efficiency Enhancers comments on the CLH proposal for 3 4 DMP.pdf

Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	11
Comment received				
The fertility effects (consistent reduction of weight of reproductive organs in several studies) are conclusive and clear and warrant a classification as Repr. 2. A classification for developmental toxicity is not warranted.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Sweden		MemberState	12
Comment received				
Fertility The dossier submitter proposes a harmonised classification as Repr. 2 for effects on fertility. The two-generation reproductive toxicity study showed a decrease in male and female reproductive organ weights at the highest dose (100 mg/kg bw/d) in both the F0 and F1 generation. However, the highest dose was set relatively low and did not elicit any general toxicity in the parental animals. Thus, it is possible that more pronounced effects could have been observed at a higher dose level. Changes in reproductive organ weights were also observed in other studies that applied higher dose levels. In addition, histopathological findings in reproductive organs were reported in females (i.e. atrophy, reduced size and/or number of functional bodies, and changes in interstitial glands) and males (i.e. spermatogenic granuloma and focal cribriform in epididymides) in repeated dose toxicity studies. We notice that the effects on fertility are similar for 3,4-dimethyl-1H-pyrazole and 3,5-dimethylpyrazole, for which the latter the Belgian CA proposed a classification as Repr. 1B for effects on fertility. The Swedish CA would welcome a clearer justification why a classification as Repr. 1B was not proposed also for 3,4-dimethyl-1H-pyrazole. Developmental toxicity The Swedish CA supports the proposal for no classification for effects on development based on the information presented in the dossier.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	13
Comment received				
Regarding reproductive organs affected by the substance (organ weight and histopathological changes), FR supports category Repr. 2 for fertility. For development, FR supports that a classification for development is not warranted.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	14
Comment received				
Due to compromised detoxification processes in the reproductive toxicity studies, the resulting internal exposure becomes irrelevant to human hazard assessment because effects occur only under experimental conditions where detoxification by excretion is impaired. Therefore, the observed effects at high doses are disproportionate and do not reflect human hazard potential. The Two-generation reproduction toxicity study showed no adverse effects on sexual function and fertility, and sex organs/reproductive systems were not adversely affected (pages 18-19). The available data from rats, mice, and dogs also showed no consistent				

effects on sex organs/reproductive systems (pages 19-22), and adverse effects observed at high dose levels where detoxification via excretion mechanisms are saturated are of lesser relevance. Available mechanistic data suggests that humans are less prone to the toxic effects of 3,4-DMP due to more efficient detoxification via excretion by the kidneys (pages 6-7). Therefore, the lead registrant suggests that a classification for effects on fertility is not justified. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMP_CLH_comments_BASF SE.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	15
Comment received				
The classifications Acute Tox. 4, H302, Acute Tox. 4, H312 and Acute Tox. 4, H332 are supported by FR.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	16
Comment received				
The registrant is in agreement with the proposed acute toxicity classifications. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMP_CLH_comments_BASF SE.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	17
Comment received				
The classifications for Acute toxicity (oral, dermal and inhalation) are clear and conclusive.				
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
12.10.2023	Germany	BASF SE	Company-Manufacturer	18
Comment received				
The lead registrant suggests to not classify for specific target organ toxicity after repeated exposure because the adverse effects observed in the nasal cavity are not relevant to humans. All other organ effects occurred either above the cut-off limit for classification or are also not considered relevant to humans due to species differences between rodents and humans (salivary gland) as discussed by the Dossier Submitter. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMP_CLH_comments_BASF SE.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	19
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
13.10.2023	Belgium	Cefic - Fertilisers Efficiency Enhancers	Industry or trade association	20
Comment received				
Regarding the proposed STOT RE category 2 (nasal cavity), we would like to quote the following provision in the CLP Regulation (Regulation (EC) 1272/2008), Annex I: " 3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to: (a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate 'significant' toxicity; (b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance; (c) changes in organ weights with no evidence of organ dysfunction; (d) adaptive responses that are not considered toxicologically relevant; (e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification Based on the above and on the available data, we suggest that 3,4- DMP should not be classified for specific target organ toxicity after repeated exposure because the adverse				

effects observed in the nasal cavity are not relevant to humans. All other organ effects occurred either above the cut-off limit for classification or are also not considered relevant to humans due to species differences between rodents and humans (salivary gland). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Fertilisers Efficiency Enhancers comments on the CLH proposal for 3 4 DMP.pdf
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	21
Comment received				
Nasal cavity effects clearly warrant STOT RE 2 classification. Other effects (e.g. liver, haematology) are not as clear and do not warrant STOT RE 2 classification.				
Dossier Submitter's Response				
RAC's response				

PUBLIC ATTACHMENTS
1. Fertilisers Efficiency Enhancers comments on the CLH proposal for 3 4 DMP.pdf [Please refer to comment No. 2, 7, 10, 20]
2. DMP_CLH_comments_BASF SE.pdf [Please refer to comment No. 1, 5, 14, 16, 18]