COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 23.10.2023

Substance name: 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate
CAS number: 202842-98-6
EC number: 424-640-9
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	1
Comment received				
A key element for DMPP hazard assessment is based on the understanding that detoxification by excretion becomes saturated between 20 and 69.2 mg/kg bw/d in rats. Toxic effects from DMPP exposure manifest at doses where internal kinetics are non-linear, resulting in internal exposures above dose proportionality. A detailed description of DMPP kinetics has been provided in pages 1-7 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. Furthermore, the DS did not evaluate the available data for serious eye damage/eye irritation (see pages 8-9) which warrants a classification for eye irritation (Cat. 2, H319). ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMPP_CLH_comments_BASF SE.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	2
Comment received				
The DE CA would like to thank the Belgian CA for assessing the toxicity of 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate 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. In section 2.1 "Proposed harmonised classification and labelling according to the CLP criteria" Table 5 the required label elements "GHS08" and "GHS07" are missing.				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Belgium	Cefic - Fertilisers	Industry or trade	3

		Efficiency Enhancers	association	
Comment received				
We would like to bring ECHA’s attention to the need of assessing DMPP 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 DMPP.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Sweden		MemberState	4
Comment received				
We thank the Belgian CA for the proposal for harmonised classification of 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate. We notice that there is no information on the toxicokinetics of the substance included in the CLH-dossier. 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 structurally similar substances (i.e. 3,5-dimethylpyrazole, 3,4-dimethyl-1H-pyrazole and 3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate).				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Belgium	Cefic - Fertilisers Efficiency Enhancers	Industry or trade association	5
Comment received				
Based on the following guidelines and on the knowledge of kinetics and internal dosimetry, along with the borderline nature of several of the findings, in our view classification for Reprotoxic Toxicity Category 1B is not justified; classification as Category 2 for fertility and classification as Category 2 for development appear more appropriate. When assessing the potential reproductive toxicity properties of DMPP, we propose considering the following: OECD 416 Guideline (adopted in 2001): "Dose levels should be selected taking into account any existing toxicity data, especially results from repeated dose studies. Any available information on metabolism and kinetics of the test compound or related materials should also be considered. In addition, this information will also assist in demonstrating the adequacy of the dosing regimen". OECD 414 guideline (adopted in 2018): "Dose levels should be selected taking into account any existing toxicity data as well as additional information on metabolism and toxicokinetics of the test substance or related materials. This information will also assist in demonstrating the adequacy of the dosing regimen". OECD 443 guideline (adopted in 2018): "Although not required, TK data from previously conducted dose range-finding or other studies are extremely useful in the planning of the study design, selection of dose levels and interpretation of results. Of particular utility are data which: 1) verify exposure of developing fetuses and pups to the test compound (or relevant metabolites), 2) provide an estimate of internal dosimetry, and 3) evaluate for potential dose-dependent saturation of				

kinetic processes. […] When selecting appropriate dose levels, the investigator should consider all available information, including the dosing information from previous studies, TK data from pregnant or non-pregnant animals, the extent of lactational transfer, and estimates of human exposure. If TK data are available which indicate dosedependent saturation of TK processes, care should be taken to avoid high dose levels which clearly exhibit saturation, provided of course, that human exposures are expected to be well below the point of saturation. In such cases, the highest dose level should be at, or just slightly above the inflection point for transition to nonlinear TK behaviour".

ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance (2017):
"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".

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

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	6
Comment received				
The fertility effects are conclusive and clear and warrant classification as Repr. 1B. The DE CA notes that it is unclear whether the historical control data (HCD) refer to the HCD range of the testing laboratory or whether those were identified otherwise (e.g. from literature or from databases of the Belgian CA). The developmental effects are conclusive and clear and warrant classification as Repr. 1B. The comparison with the CLP criteria (section 10.10.6.) would benefit from a discussion on maternal toxicity. The information is provided in the study summaries under 10.10.5.				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	7
Comment received				
Fertility: FR considers that this case is borderline between categories Repr. 1B and Repr. 2 for fertility. For female fertility, in the section comparison to CLP criteria, could you please add information on how you considered general toxicity? In the two-generation reproductive toxicity study (2004), there are some concerns regarding the adrenal gland. Indeed, in the F0 generation, adrenal weight was increased in males and there were hypertrophy of this organ in both sexes. Furthermore, in the F1 generation, adrenal weight was increased in both sexes and atrophy was also observed in both sexes. These data were also observed in males in the repeated dose 28-ays oral toxicity study (1997) and in the OECD TG408 study. In the pre and post-natal developmental toxicity study in rats (2013), hormonal changes				

were observed: a dose-related decreased in 11-Deoxy-corticosterone and progesterone hormones. Adrenal gland is an endocrine organ. The decrease in the concentration of corticosterone, accompanied by a decrease in the level of its precursor progesterone, could indicate suppression of steroidogenesis. Did you consider the relevance of an ED classification?

- Development:
FR agrees with the classification proposal repr.1B, H360D. Could you please discuss maternal toxicity in the section comparison to CLP criteria?

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Sweden		MemberState	8
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, which describes clear evidence of effects on male and female fertility in the two-generation reproductive toxicity study. To increase the robustness of the assessment we would welcome a clarification of whether there were any relevant adverse clinical signs among the parental animals of this study, in addition to the decreased food consumption and body weight. Developmental toxicity The Swedish CA supports the proposed classification as Repr. 1B for effects on development based on the information presented in the dossier. There is clear evidence of developmental toxicity, including a decrease in the viability index and the number of delivered pups as well as an increase in the number of dead pups reported in several studies.				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	United Kingdom	Health and Safety Executive	National Authority	9
Comment received				
DMPP: Hazard class: Reproductive Toxicity (Sexual Function and fertility) 'The DS has proposed classification for sexual function and fertility category 1B on the basis of reduced female fertility index and associated fertility parameters (oestrous cycle, mean mating day until DPC) at 500 mg/kg bw/d in the two generation reproductive toxicity study (2004). Furthermore, several males failed to mate or mate and fail to get the females pregnant (plus some reductions in reproductive organ weights). It is unclear, however, from the CLH report and associated annex, the role that maternal toxicity has played at this dose level. The DS noted high maternal toxicity and developmental toxicity as the reason for lowering the top dose to 300 mg/kg bw/d for a second mating. No further reference to this 'high maternal toxicity' is made again. Therefore, could the DS clarify the extent of this toxicity and the potential impact it may have had on sexual function and fertility?'				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Netherlands		MemberState	10
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?

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	11

Comment received

It is important to understand the internal dosimetry context for the reproductive toxicity studies used for DMPP hazard assessment. The toxic effects observed in rats are observed only where saturation of detoxification via excretion is present. Results from the Two-generation Reproductive Toxicity study are summarized on pages 9-16, with additional studies of potential value for reproductive hazard assessment summarized on pages 16-18. Within the two-generation reproductive toxicity study, the second mating performed with the same F0 group following a reduction in exposure demonstrates that the initial observation of impaired fertility in F0 rats was not a persistent effect, but rather a secondary non-specific consequence of the increasing internal dose due to saturated excretion kinetics. Marginal effects on fertility in the F1 rats should be considered in light of historical control data along with non-treatment related and incidental findings in reproductive organs found in mating partners for two of the five mating pairs.
Based on the knowledge of kinetics and internal dosimetry, along with the borderline nature of several findings, classification as Category 2 for fertility appears more appropriate.
Assessment of potential for developmental effects should be considered in the context of kinetics in the rat. Doses resulting in fetal or pup mortality in the two-generation study (see pages 20-24) and phosphate metabolism study (page 34) exceeded the capacity for detoxification by excretion and are thus of doubtful relevance for human health hazard assessment.
A pre- and post-natal developmental toxicity test in rats did not replicate the reduced peri- and early postnatal pup mortality, increased number of stillborn pups, slightly reduced live

birth indices and the reduced number of delivered pups per dam observed in the two-generation reproductive toxicity test (pages 25-27).
The OECD 414 guideline study in rats (pages 27-32) found no teratogenic effects. Evidence for developmental toxicity was only observed at 400 mg/kg bw/day, a dose in excess of excretion capacity, and was limited to slightly lower mean placental and mean fetal body weights, statistically significantly increased rates for fetal skeletal variations and delays in fetal skeletal maturation, which were associated with reduced fetal body weights. These effects are of insignificant to low relevance for developmental hazard classification.
Due to the saturation of detoxification by excretion, there is reason to doubt the human relevance of developmental effects observed in DMPP-exposed rats. On that basis, classification in Category 2 for development appears more appropriate.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMPP_CLH_comments_BASF SE.pdf

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	12
Comment received				
Classification for Acute Oral Toxicity in Category 4 appears appropriate, but the proposed Acute Toxicity Estimate of 500 mg/kg bw/d appears too conservative. Repeated dose toxicity studies in rats and mice were performed at doses in excess of 500 mg/kg bw/d, even up to 1103 mg/kg bw/d, without mortality (summarized on page 8 of the attached comments). This strongly suggests a greater value is justified. An Acute Toxicity Estimate value of 750 mg/kg bw/d would be better justified. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMPP_CLH_comments_BASF SE.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	13
Comment received				
Acute Tox. 4, H302: This classification is supported by FR				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Belgium	Cefic - Fertilisers Efficiency Enhancers	Industry or trade association	14
Comment received				
Classification for acute oral toxicity in Category 4 appears appropriate, but the proposed acute toxicity estimate of 500 mg/kg bw/d appears too conservative. An acute toxicity estimate value of 750 mg/kg bw/d would be better justified based on the references above. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Fertilisers Efficiency Enhancers comments on the CLH proposal for DMPP.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Finland		MemberState	15
Comment received				

Acute Toxicity – oral: Based on the available results from the only available study, the LD50 was comprised between 200 and 2000 mg/kg bw. Two of the three tested animals died at the dose level of 2000 mg/kg bw, so it can be concluded that LD50 is below that. Therefore, the FI CA agrees that the available data supports classification as Acute Tox.
The criteria for Acute Tox (oral) from CLP regulation (Regulation (EC) No 1272/2008) are 50 < ATE ≤ 300 for Category 3 and 300 < ATE ≤ 2 000 for Category 4. Therefore, based on the available data, and considering the fact that all 3 female rats exhibited clinical signs with the dose of 200 mg/kg bw, there remains some uncertainty whether the Acute Tox category should be 3 or 4.
As only a range of LD50 was available, an ATE of 500 mg/kg bw is warranted with classification of Acute Tox. Cat. 4 based on the table 3.1.2 of the CLP regulation.

We agree that based on the available results, no classification for acute dermal toxicity or acute inhalation toxicity is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	16
Comment received				
The classification for Acute toxicity is clear and conclusive.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	France		MemberState	17
Comment received				
STOT RE 2, H373: This classification is supported by FR				

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2023	Belgium	Cefic - Fertilisers Efficiency Enhancers	Industry or trade association	18
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 classification concerning				

specific target organ toxicity after repeated exposure is not justified, as the adverse effects observed in the nasal cavity are not relevant to humans.

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

Date	Country	Organisation	Type of Organisation	Comment number
12.10.2023	Germany	BASF SE	Company-Manufacturer	19
Comment received				
It is proposed that nasal toxicity in rats results from transport of a DMPP metabolite into the nasal epithelium, causing cellular toxicity that results in degeneration and regeneration in the tissue. DMPP metabolite transport into the rat nasal epithelium is mediated by Organic Anion Transporter 6, a gene that is not expressed in humans, thus it is plausible the nasal effects are a rodent-specific mechanism (page 38). Where a rodent-specific mechanism is reasonably certain, classification under CLP is not justified. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DMPP_CLH_comments_BASF SE.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2023	Germany		MemberState	20
Comment received				
Nasal cavity effects clearly warrant STOT RE 2 classification. Liver effects clearly do not warrant STOT RE 2 classification. It is unclear why diffuse atrophy in the mandibular glands was not discussed in more detail in section 10.12.2.				

PUBLIC ATTACHMENTS
1. Fertilisers Efficiency Enhancers comments on the CLH proposal for DMPP.pdf [Please refer to comment No. 3, 5, 14, 18]
2. DMPP_CLH_comments_BASF SE.pdf [Please refer to comment No. 1, 11, 12, 19]