Helsinki, 09 December 2020

Addressees

Registrants of 3-methylpyrazole listed in the last Appendix of this decision (registrant(s)[1])

Decision/annotation number

[For the final decision] Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)

Registered substance subject to this decision, hereafter 'the Substance'

Substance name: 3-methylpyrazole
EC number: 215-925-7
CAS number: 1453-58-3

DECISION ON SUBSTANCE EVALUATION

Under Article 46(1) of Regulation (EC) No 1907/2006 (REACH), you must submit the following information on the Substance:

Human health and environment

Request 1

Alcohol dehydrogenase inhibition *in vitro* assay with the Substance as further specified in Appendix 1;

The test must be performed according to the test method described in Li and Theorell, (1969) *Human Liver Alcohol Dehydrogenase: Inhibition by Pyrazole and Pyrazole Analogs*. Acta Chemica Scandinavia, 23: 892-902, with the following specifications:

- 4-methylpyrazole (4-MP), a structurally similar substance, shall be used as positive control

- The Substance shall be tested at 3 concentrations: 1 µM, 10 µM and 100 µM

Commercial kits can also be used, as far as similar information is obtained from them. The use of human liver ADH is the preferred option (as applied in Li and Theorell, 1969), but rodent liver ADH or recombinant ADH can also be used.

[1] The terms registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

Deadline to submit the requested information

Appendix 1: Section 3 provides further details of how the deadlines were derived.

You must provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the chemical safety report by the deadline indicated below.

In addition to the robust study summaries, you must submit the full study report for Request 1 by the same deadline, by attaching it to the relevant endpoint study record in IUCLID.

The information required shall be generated and provided by **15 December 2021** from the date of the decision.

Appendices

The reasons of this decision and any further test specifications of the requirements are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

Who performs the testing?

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study on behalf of all registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

Appeal

This decision may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information**.**

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[2] by Christel Schilliger-Musset, Director of Hazard Assessment

[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Basis for substance evaluation

The objective of substance evaluation under REACH is to allow for the generation of further information on substances suspected of posing a risk to human health or the environment ('potential risk').

ECHA has concluded that further information on the Substance is necessary to enable the evaluating Member State Competent Authority (MSCA) to clarify a potential risk and whether regulatory risk management is required to ensure the safe use of the Substance.

The ECHA decision requesting further information is based on the following:

(1) There is a potential risk to human health or the environment, based on a combination of hazard and exposure information;
(2) Information is necessary to clarify the potential risk identified; and
(3) There is a realistic possibility that the information requested would allow improved risk management measures to be taken.

The Appendix 1 entitled 'Reasons to request information' describe why the requested information are necessary and appropriate.

Appendix 1: Reasons to request information to clarify the potential risk related to Endocrine disruption.

Based on the evaluation of all relevant information submitted on 3-methylpyrazole and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State competent authority (MSCA) to complete the evaluation of whether the Substance constitutes a risk to human health and/or the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in another decision to clarify the concern, according to Article 46(3) of REACH.

1 The potential risk – human health and environment

The identification of a potential risk is based on a combination of exposure and hazard information.

According to information in the registration dossier the Substance is used as nitrification inhibitor in fertilisers. The Substance has wide dispersive use in the following areas: agriculture, forestry and fishing. Thus significant exposure to workers and the environment cannot be excluded.

Based on information in the registration dossier and information from the published literature as detailed below, there is a concern that the Substance may be an endocrine disruptor (ED) for human health and/or the environment according to the World Health Organisation/International Programme on Chemical Safety working definition (WHO/IPCS, 2002).

Based on this exposure and hazard information, there is a potential risk for workers, man via the environment and for the environment. As the available information is not sufficient to conclude on potential ED properties, further information is needed, as explained below.

2 The possible risk management measures – human health and environment

The substance is currently only self-classified in the registration dossier(s) as Acute Tox. 4, Skin Corr. 1B, Eye Damage 1, Repr. 2.

There is however also a RAC opinion from November 2019, for a Repr. 1B harmonized

classification (together with Acute Tox. 4, STOT RE 2, Skin Corr. 1 and Eye Dam. 1).[3]

If the obtained data from Request 1 are sufficient to confirm the suspected ED properties as defined by WHO/IPCS (WHO/IPCS, 2002) the evaluating MSCA will assess the need for further regulatory risk management in the form of identification as a substance of very high concern (SVHC) under Article 57(f) of REACH in addition to Article 57(c) and subsequent regulatory measures.

This may lead to stricter risk management measures than those currently in place. Especially, if the substance is recognised as endocrine disruptor, no safe threshold could be considered and exposure should be avoided.

[3] https://echa.europa.eu/nl/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e182ed4264

REQUEST 1 (Alcohol dehydrogenase inhibition *in vitro* assay): The concern(s) identified

Information on adverse effects:

Developmental toxicity

Developmental effects including severe fetal malformations in the urogenital tract and/or in the cardiovascular system have been observed in 3 different prenatal developmental toxicity studies. These effects cannot be explained by maternal toxicity.

- In a developmental prenatal toxicity study (registration dossier (study report, 1992)), performed following the OECD TG 414, groups of 25 pregnant rats were exposed to 0, 15, 45 or 90 mg/kg bw/day of the Substance, from gestational day (GD) 6 to 15. Dams exhibited only a significant decrease of body weight at the highest dose level (90 mg/kg bw/d). At this dose level, an increased incidence of fetal malformations in the urogenital tract and/or in the cardiovascular system was observed (14 fetuses at the highest dose vs 0 in control group).These effects consisted of an increased incidence of efferent urinary tract severely dilated, agenesie of kidney(s), agenesie of ureter(s), malformation of great vessels (displaced aortic arch) and dilatation of both ventricles. Furthermore, skeletal malformations were also observed and were outside the range of the historical control data (such as thoracic vertebral body/bodies dumbbell-shaped and/or bipartite). In addition, a significant decrease of the fetal body weight was observed at the mid and high dose levels (45 and 90 mg/kg bw/d).

- Moreover, in another developmental toxicity study (Bleyl DWR, 1990), which does not follow an OECD guideline, groups of pregnant rats (number of animals unspecified) were exposed, on GD 10 and 11, to the Substance at a concentration of 0, 20, 40, 80 or 160 mg/kg bw/d. Dams did not show any maternal toxicity (no effects observed on the body weight or the liver weight, no more information available). Nevertheless, the rate of living pups at birth was significantly reduced at 160 mg/kg bw/day (77% compared to the control group) and most of the living pups died during the first day of life (the survival index at PND4 was of 26%). Necropsy of these fetuses revealed an urogenital syndrome. Furthermore, in the mid dose group, 15.6% of the living pups exhibited also this urogenital syndrome

(uni or bilateral kidney agenesis, hydronephrosis, undescended testis).

- In another developmental toxicity study (anonymous, 1984), not following a guideline, groups of pregnant rats were given by gavage the Substance at a concentration of 0, 50, 100, 200 and 400 mg/kg bw/day. Animals were exposed at GD 1, 4, 10, 13, 18 and 20. Dams exhibited a significant lower body weight value at 200 and 400 mg/kg bw/d. At 200 mg/kg bw/d, the body weight value was only significantly decreased at GD 20 whereas at 400 mg/kg bw/d the value was significantly lower already at GD 13. Regarding the foetal examination, a dose dependent increase of the malformation rate was noted (0.5, 2.0, 11.1, 46.8** and 100**% at 0, 50, 100, 200 and 400 mg/kg bw/d, respectively). Amongst these malformations, a significant increase in the incidence of urogenital syndrome (0, 0, 4.4, 40.8** and 58.8**% at 0, 50, 100, 200 and 400 mg/kg bw/d, respectively) and an increase in the incidence of cleft palate (0.5 and 12.5% at 200 and 400 mg/kg bw/d, respectively) were observed. Moreover, a significant increase in the incidence of post-implantation loss were observed at 400 mg/kg bw/d (74.9**% vs 11.5% in control group).

In another prenatal developmental toxicity study (anonymous, 1989), not following a guideline, groups of 8 pregnant rats received by gavage the Substance at a concentration of 0, 25, 100, 175 and 225 mg/kg bw/day. Animals were exposed from GD 6 to 18. 6 out of 8 dams exposed to 175 mg/kg bw/d and all dams exposed to 225 mg/kg bw/d died or were sacrificed prematurely. The 2 surviving animals exposed to 175 mg/kg bw/d had no live fetuses. At 100 mg/kg bw/day, moderate to severe decrease in body weight was noted in dams and in their fetuses. One fetus of this group exhibited a cleft palate.

Potential effects on fertility could not be assessed as there is no reproductive toxicity study available (e.g. OECD TG 416, 421, 422 or 443) in the registration dossier and no significant effects on the reproductive organs were observed in the repeated dose toxicity studies.

Information on the potential mode of action (MoA)

Retinoic acid (RA) is essential for reproduction and for many events in the developing embryo, including kidney and cardiovascular development (Clagett-Dame & Knutson, 2011). The alcohol dehydrogenase (ADH) is a key enzyme in the biosynthesis of RA.

RA, the active form of Vitamin A, is synthesised from retinol in two steps, by two enzymes:
1° Retinol/Alcohol dehydrogenase (RDH/ADH) (reversible, rate-limiting step) and
2° Aldehyde dehydrogenase (ALDH) (irreversible step) (Duester, 1996)

Retinol	→ 1° ←	retinal	→ 2°	retinoic acid (RA)

A tightly controlled level of RA in tissues is essential. Too much or too little of RA is equally harmful, the levels of RA in tissues have to be tightly controlled. RA is essential for normal regulation of a wide range of biological processes. It is essential in the development and function of several organs systems (including the development of the brain, heart and kidney). Deregulated retinoid signaling can contribute to serious diseases. For example, RA is necessary for renal development and even mild gestational Vitamin A deficiency can affect nephron endowment (Das et al., 2014).

Several pyrazoles have been found to be potent inhibitors of human liver ADH (Li and Theorell, 1969). Among the tested pyrazoles, the mono-substituted ones were the more potent (inhibition potency of 4-iodopyrazole > 4-methylpyrazole > 4-bromopyrazole > pyrazole). The di-substituted derivatives were not more effective than pyrazole itself and tribromopyrazole was less inhibitory than pyrazole (see details for pyrazole and 4-methylpyrazole below in section 4). The Substance was not tested for ADH inhibition.
4-methylpyrazole (EC 231-445-0, CAS 7554-65-6)(4-MP), which is structurally similar to this Substance, is used as pharmaceutical ("*fomepizole*") in case of ethylene glycol or methanol poisoning, due to its demonstrated capability to inhibit alcohol dehydrogenase (ADH) (Mégarbane, 2010, Blomstrand et al., 1979).

4-MP is registered under REACH for intermediate use only. No reproductive toxicity study is available in the registration dossier.

Moreover, it has been shown that intraperitoneal injection of 4-MP in mice significantly decreases the number and development of oocytes ovulated in response to human chorionic gonadotropin/LH. Those effects were clearly linked to inhibition of RA synthesis, since injection of retinoic acid completely reversed the effects of 4-MP (Kawai et al., 2016).

Given the ADH inhibitory properties of the structurally similar substance 4-MP, the role of ADH in RA synthesis and the essential role of RA in reproduction and development, the observed adverse developmental effects of the Substance raise a concern for endocrine disruption via the retinoic acid pathway.

Several different ADH isoenzymes, but also retinoic acid dehydrogenase (RoDH) enzymes (the later belonging to the short chain dehydrogenases/reductase (SDR) family) were shown to oxidize retinol *in vitro* (reviewed by Kedishvili, 2016).
The response of the genes encoding retinol dehydrogenases may be cell context-dependent (Kedishvili, 2016). Therefore, we cannot exclude that developing embryos could be more sensitive to inhibition of RA production compared to reproductive organs in adults.

REQUEST 1 (Alcohol dehydrogenase inhibition *in vitro* assay): Why new information is needed

Information both on endocrine activity and adverse effects, are required to conclude on the endocrine disrupting properties (WHO/IPCS, 2002). As described above, the Substance causes adverse effects on development, which may be a consequence of disturbance of the retinoic acid pathway via inhibition of ADH. The available data shows that substances structurally similar to the Substance significantly inhibit human ADH, but currently there is no information available on rodent and/or human ADH inhibition potential of the Substance.

In order to conclude that there is a biologically plausible link between the observed adverse effects on pre-natal development in the studies with the Substance and disruption of the retinoic acid pathway, information on whether or not the Substance can inhibit the human and/or rodent ADH enzyme is required. Therefore, the requested information is needed to clarify the concern.

REQUEST 1 (Alcohol dehydrogenase inhibition *in vitro* assay): Considerations on the test method

The requested study will provide information on the inhibition of ADH by the Substance.
You must determine enzymatic activity of ADH in the absence and presence of the Substance, by monitoring the production of NADH by spectrophotometry (change in

absorbance) (following the method described in Li and Theorell, 1969). Kinetics of NAD+ reduction by ethanol shall be observed using a sensitive filter fluorimeter to measure the fluorescence of NADH, after calibration of the instrument with known concentrations of NADH. The inhibitory activity of the Substance towards ADH shall be assessed and compared to the well known inhibitory activity of 4-MP (used as positive control).

Specifications of the test method (in addition to test method described in Li and Theorell, 1969):

- 4-MP EC Nr. 231-445-0 (at 1 µM and 10 µM) shall be used as positive control.
- The Substance must be tested at 3 concentrations: 1 µM, 10 µM and 100 µM.

Commercial kits can also be used, as far as similar information is obtained from them.

Use of human liver ADH is the preferred option (as used in Li and Theorell, 1969), but rodent liver ADH or recombinant ADH can also be used. Indeed, orthologs of human enzymes involved in retinol oxidation were found in mouse and frog (Kedishvili, 2016). Retinol dehydrogenase activity is therefore conserved from lower vertebrates to humans.

In your comment, you agree to conduct the requested test with the registered substance. Since there is no validated guideline available for this non-standard test method you mentioned some uncertainties regarding the correct performance of the test. You presented 2 options :

Option 1 - the use of recombinant ADH from a commercial kit available from Sigma Aldrich for Alcohol Dehydrogenase Activity Assay;

Option 2 - the use of commercial liver extracts (S9 fraction or microsomes; both human and rat), which are not characterized in terms of ADH content.

ECHA considers it scientifically acceptable to use recombinantly expressed ADH, as well as ADH from human or rat liver. ECHA agrees that the use of a recombinant ADH enzyme of the Sigma kit is an appropriate test and better compared to the option 2 using S9 or other microsomal fractions, which would make validation more complex.

You must submit the full study report for the requested study. Considering the non-standard method requested, a complete rationale of test design and interpretation of

results and access to all information available in the full study report (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) are needed. This will allow the evaluating MSCA to fully assess all the provided information, including the statistical analysis, and to efficiently clarify the concern for endocrine activity.

REQUEST 1 (Alcohol dehydrogenase inhibition *in vitro* assay): Alternative approaches and proportionality of the request

The request for this *in vitro* assay is suitable and necessary to obtain information that will allow to clarify whether there is a potential risk for human health and the environment. More explicitly, between different available alternatives it is the least onerous way to obtain information. The possible alternative of testing the inhibition of retinoic acid biosynthesis *in vivo* requires more animals, is more expensive and is not considered necessary, in view of the already available data. Moreover, there is currently no standard *in vitro*/*in vivo* test available which would address specifically the inhibition of retinoic acid biosynthesis.

3 Consideration of the time needed to perform the requested studies

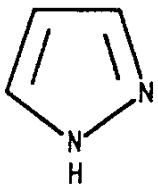
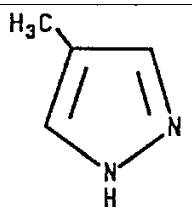
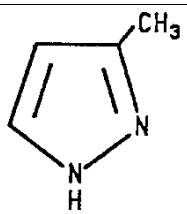
The deadline for provision of the requested data takes into account the time that you may need to agree on which of the registrant(s) will perform the required tests (3 months is allocated for this) and include the time required for developing an analytical method, conduct of the study, preparation of the study report and reporting in IUCLID.
For Request 1, ECHA considers that 6 months is a sufficient time for conduct and reporting of the *in vitro* study.

4 Explanation of the Grouping of substances applied for the substance evaluation

Relevant data were available in the literature on 4-MP, a structurally similar substance. Those data were therefore taken into account during the substance evaluation of the Substance. Pyrazole and 6 derivatives were tested for inhibition of human liver ADH (data from Li and Theorell, 1969). The Substance was not tested in this study.

There are data showing similar inhibitory activity of 4-MP and the Substance in another oxido-reduction enzymatic reaction: the Substance is used in fertiliser, as nitrification

inhibitor (registration dossier). 4-MP is also an effective inhibitor of ammonium oxidation in soil (McCarty and Bremner, 1989) (see values in the table below). Nitrification inhibitor suppressed oxidation of ammonium to nitrite (first step of nitrification) by Nitrosomas bacteria for a few days to weeks (Zerulla et al., 2001).

		Pyrazole	**4-methyl-pyrazole**	**The Substance**
CAS Nr		288-13-1	7554-65-6	1453-58-3
EC Nr		206-017-1	231-445-0	215-925-7
Structure				
Inhibition of human LADH	**1** µM	93%	58%	Not tested
	10 µM	63%	14%	Not tested
Inhibition of nitrification (in different soils: Harps-webster-storden)	**0.01** µmol g-1 soil	23%-27%-31%	27%-44%-63%	38%-43%-73%
	0.1 µmol g-1 soil	57%-58%-92%	55%-57%-92%	45%-46%-84%
	0.5 µmol g-1 soil	94%-97%-99%	93%-81%-95%	84%-76%-93%

5 References

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Blomstrand R., Ostling-Wintzell H, LoF A., McMartin K., Tolf B-R. and Hedstrom k-G. (1979). Pyrazoles as inhibitors of alcohol oxidation and as important tools in alcohol research: An approach to therapy against methanol poisoning. Proc. Nati. Acad. Sci. USA, 76(7): 3499-3503

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Duester G. (1996). Involvement of alcohol dehydrogenase, short-chain dehydrogenase/reductase, aldehyde dehydrogenase, and cytochrome P450 in the control of retinoid signaling by activation of retinoic acid synthesis. Biochemistry, 35 (38): 12221–12227.

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Zerulla W., Barth T., Dressel J., Erhardt K., Horchler von Locquenghien K., Pasda G., Rädle M., Wissemeier A. (2001). 3,4-Dimethylpyrazole phosphate (DMPP) – a new nitrification inhibitor for agriculture and horticulture. Biology and Fertility of Soils, 34(2): 79–84.

Appendix 2: Procedural history

This decision does not imply that the information you submitted in your registration dossier(s) are in compliance with the REACH requirements. ECHA may still initiate a compliance check on your dossiers.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Suspected Reprotoxic, Potential endocrine disruptor, Exposure of environment, Wide dispersive use, 3-methypyrazole CAS No 1453-58-3 (EC No 215-925-7) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2018. The updated CoRAP was published on the ECHA website on 20 March 2018. The competent authority of Belgium (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the endocrine concern. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 18 March 2019.

Decision-making

ECHA notified you of the draft decision and invited you to provide comments.

ECHA received your comments and forwarded them to the evaluating MSCA.

For the purpose of this decision-making, dossier updates made after the date the draft of this decision was notified to you (Article 50(1) of REACH) will not be taken into account.

The evaluating MSCA took your comments into account (see Appendix 1).

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Articles 52(2) and 51(3) of REACH.

After the deadline set in this decision has passed, the evaluating MSCA will review the information you will have submitted and will evaluate whether further information is still needed to clarify the potential risk, according to Article 46(3) of REACH. Therefore, a subsequent evaluation of the Substance may still be initiated after the present substance evaluation is concluded.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to otherwise fulfil the information request (s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the required experimental study/ies, the sample of the substance to be used ('test material') has to have a composition that is within the specifications of the substance composition that are given by all registrant(s). It is the responsibility of all the registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on the composition of the test material. The substance identity information of the Substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who will carry out the study on behalf of the other registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at: https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspxF
Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing
If ECHA is not informed of such agreement within 90 days, it will designate one of the registrants to perform the stud(y/ies) on behalf of all of them