Assessment of regulatory needs

Authority: European Chemicals Agency

Date: 7 December 2021

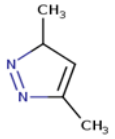
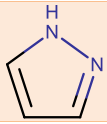
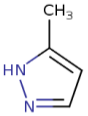
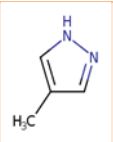
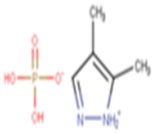
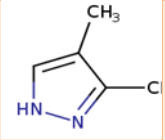
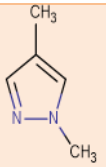
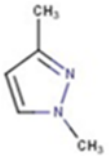
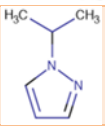
Group Name: Pyrazoles

Chemical structure: -

Revision history

Version	*Date*	*Description*
1.0	07/12/2021	

Substances within this group:

EC / List number	CAS number	Substance name (acronyms)	Chemical structures	Registration type (full/OSII or TII/NONS), highest tonnage band among all the registrations (t/y)[1]
Sub-group 1: C-alkylated pyrazoles				
200-657-5	67-51-6	3,5-dimethylpyrazole (3,5-DMP)		Full, 100-1000
206-017-1	288-13-1	Pyrazole (Pz)		Full, not (publicly) available
215-925-7	1453-58-3	3-methylpyrazole (3-MP)		Full, 100-1000
231-445-0	7554-65-6	4-methylpyrazole (4-MP)		OSII or TII
424-640-9	202842-98-6	1H-Pyrazole, 3,4-dimethyl-, phosphate (1:1)		Full, 100-1000
429-130-1	2820-37-3	3,4-dimethyl-1H-pyrazole (3,4-DMP)		NONS
Sub-group 2: N-alkylated pyrazoles				
600-813-6	1072-68-0	1H-pyrazole, 1,4-dimethyl- (1,4-DMP)		OSII or TII
689-662-5	694-48-4	1,3-dimethyl-1H-pyrazole (1,3-DMP)		OSII or TII
823-314-7	18952-87-9	1-isopropyl-1H-pyrazole (1-iPP)		OSII or TII

[1] Note that the total aggregated tonnage band may be available on ECHA's webpage at https://echa.europa.eu/information-on-chemicals/registered-substances

Contents

DISCLAIMER

The author does not accept any liability with regard to the use that may be made of the information contained in this document. Usage of the information remains under the sole responsibility of the user. Statements made or information contained in the document are without prejudice to any further regulatory work that ECHA, the Member States or other regulatory agencies may initiate at a later stage. Assessments of regulatory needs and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment.

Foreword

The purpose of the assessment of regulatory needs of a group of substances is to help authorities conclude on the most appropriate way to address the identified concerns for a group of substances or a single substance, i.e. the combination of the regulatory risk management instruments to be used and any intermediate steps, such as data generation, needed to initiate and introduce these regulatory measures.

An assessment of regulatory needs can conclude that regulatory risk management at EU level is required for a (group of) substance(s) (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. While the assessment is done for a group of substances, the (no) need for regulatory action can be identified for the whole group, a subgroup or for single substance(s).

The assessment of regulatory needs is an important step under ECHA's Integrated Regulatory Strategy. However, it is not part of the formal processes defined in the legislation but aims to support them.

The assessment of regulatory needs can be applied to any group of substances or single substance, i.e., any type of hazards or uses and regardless of the previous regulatory history or lack of such. It can be done based on different level of information. A Member State or ECHA can carry out this case-by-case analysis. The starting point is available information in the REACH registrations and any other REACH and CLP information. However, more extensive set of information can be available, e.g. assessment done under REACH/CLP or other EU legislation, or can be generated in some cases (e.g. further hazard information under dossier evaluation). Uncertainties associated to the level of information used should be reflected in the documentation. It will be revisited when necessary. For example, after further information is generated and the hazard has been clarified or when new insights on uses are available. It can be revisited by the same or another authority.

The responsibility for the content of this assessment rests with the authority that developed it. It is possible that other authorities do not have the same view and may develop further assessment of regulatory needs. The assessment of regulatory needs does not yet initiate any regulatory process but any authority can consequently do so and should indicate this by appropriate means, such as the Registry of Intentions.

For more information on Assessment of regulatory needs please consult the ECHA website[2].

[2] https://echa.europa.eu/understanding-assessment-regulatory-needs

Glossary

CCH	Compliance Check
CLH	Harmonised classification and labelling
CMR	Carcinogenic, mutagenic and/or toxic to reproduction
DEv	Dossier evaluation
ED	Endocrine disruptor
NONS	Notified new substances
OEL	Occupational exposure limit
OSI or TII	On-site isolated intermediate or transported isolated intermediate
PBT/vPvB	Persistent, bioaccumulative and toxic/very persistent and very bioaccumulative
RMOA	Regulatory management options analysis
RRM	Regulatory risk management
SEv	Substance evaluation
STOT RE	Specific target organ toxicity, repeated exposure
STOT SE	Specific target organ toxicity, single exposure
SVHC	Substance of very high concern

1 Overview of the group

ECHA has grouped together structurally similar substances based on the presence of the pyrazole moiety. The scope of this group is substances with a non-condensed pyrazole ring substituted with a short chain aliphatic alkyl group and lacking any other functional groups that may introduce other reactivity or interactions. The group pyrazoles, is composed of 9 members. Division in subgroups 1 (C-alkylated pyrazoles) and 2 (N-alkylated pyrazole is based on structural differences (C vs. N bound pyrazoles), differences in hazard profile and reactivity.

Analysis of the available information in the registration dossiers of the substances in subgroup 1 reveals several reproductive toxicity related findings on fertility and on development.

In addition, the Committee for Risk Assessment (RAC) agreed to a harmonised classification (CLH) proposal to classify 3-MP as toxic to reproduction category 1B H360D (opinion adopted at RAC 51, December 2019), which is now included in the Annex VI to the CLP Regulation with it's 17th amendment[3].

Based on information reported in the REACH registration dossiers, the most relevant sector of use is use as fertiliser (3-MP and EC 424-640-9), 3-MP used as a nitrification inhibitor in fertiliser. In addition to formulation and industrial uses, uses in fertilisers are reported for professional workers (3-MP; EC 424-640-9 and consumers (EC 424-640-9). Potential for exposure to human health cannot be excluded in professional and consumer uses; neither can releases to the environment for uses in fertilisers.

Other substances in the group are used in the polymers sector (3,5-DMP; production and modification of polymers), in the pharmaceutical industry (Pz; manufacture of active pharmaceutical ingredients (APIs)) and in the electronics sector (Pz; wafer coating).

Some of the substances in subgroup 1 and all three substances in subgroup 2 (N-alkylated pyrazoles) are also used as intermediates in other chemical reactions (not further specified in the registration dossiers).

[3] Harmonised classification as Repr. 1B, Acute Tox. 4, STOT RE 2, Skin Corr. 1, Eye Dam. 1 (H360D, H302, H373 (lung), H314, H318) (https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32021R0849&from=EN)

Note on the scope of ECHA's assessment of regulatory needs

Regarding hazards, the focus of ECHA's assessment is on CMR (carcinogenic, mutagenic and/or toxic to reproduction), sensitiser, ED (endocrine disruptor), PBT/vPvB or equivalent (e.g. substances being persistent, mobile and toxic), aquatic toxicity hazard endpoints and therefore only those are reflected in the table in section 3. This does not mean that the substances do not have other known or potential hazards. In some specific cases, where ECHA identifies a need for regulatory risk management action at EU level for other hazards (e.g. neurotoxicity, STOT RE), such additional hazards may be addressed in the assessment. An overview of classification is presented in Annex 1.

On the exposure side, ECHA is mainly using the information on uses reported in the registration dossiers (IUCLID) as a proxy for assessing the potential for exposure to humans and releases to the environment. The potential for release / exposure is generally considered high for "widespread" uses, i.e. professional and consumer uses and uses in articles. For these uses, normally happening at many places, the expected level of control is *à priori* considered limited. The chemical safety reports are not necessarily consulted and no quantitative exposure assessment is performed at this stage.

2 Justification for the need for regulatory risk management action at EU level

Based on currently available information, there is a need for (further) EU regulatory risk management – restriction for reproductive toxicity, ED, and potential P/vP properties and mobility due to the potential for release and exposure of the substances (ECs 215-925-7, 424-640-9, 429-130-1, 206-017-1, 231-445-0 and 200-657-5 (the latter without ED) used as fertiliser in the sub-group 1 (C-alkylated pyrazoles).

The following members of the sub-group 1 are used as fertilisers: 3-MP (EC 215-925-7) and EC 424-640-9. The other members in this sub-group are not currently used in fertilisers but based on their chemical structures could be used as potential alternatives in fertilisers.

Based on ECHA's assessment of currently available hazard information, most of the substances in sub-group 1, with the exception of Pz (EC 206-017-1) and 4-MP (EC 231-445-0), are self-classified as Repr. 2 H361. Information in the registrations dossiers is sufficient to support classification for Repr. 1B H360D and/or F for 3,5-DMP (EC 200-657-5); EC 424-640-9 and 3,4-DMP (EC 429-130-1 read across from EC 424-640-9) and therefore a proposal for harmonised classification. This is further supported by the inclusion of the 3-MP classification as Repr. 1B H360D in Annex VI of the CLP Regulation. The available information in the registration dossiers for Pz and 4-MP are not sufficient to enable conclusions on reproductive toxicity and therefore do not allow for a proposal for harmonised classification to be made. However, there are indications for reproductive effects of such substances and given the structural similarity to the other data rich group members, read-across could be considered.

Furthermore, all members of this sub-group (with the exception of the 3,5-DMP) have also reported endocrine effects (thyroid, adrenal glands, levels of testosterone and estradiol). Given the structural resemblance between the members of the group it is expected that there is an underlying common mechanism that could be

used for read across, however there is not enough evidence at this point to support this assumption.

The substances in this sub-group are not readily biodegradable and therefore fulfils the P/vP screening criteria, have low bioaccumulation potential (log Kow <3; low experimental BCF value for one substance) but are expected to be mobile in the environment. Substances in this sub-group have potential for exposure to both consumers and professionals and releases to the environment in particular from the use as fertilisers. Compliance check is proposed for some of the substances in particular to clarify the potential P/vP properties.

The combination of potential for exposure to humans, releases to the environment and both human health (reproductive toxicity and ED) and environmental (P/vP and mobility) hazards is clearly of concern and therefore it is proposed to consider restriction of the use of these substances in fertilisers.

The fertilisers regulation (EU 2019/1009) alone does not seem to be sufficient to address these (potential) hazards. The regulation does not contain a specific clause that would prevent the use of substances having reproductive toxicity, ED properties or being P/vP and mobile in fertilisers and it states that the safety of its constituent substances for use in fertilisers should be established through REACH registration.

The first step of the regulatory risk management action proposed, should the hazard be confirmed, is the confirmation of hazard via harmonised classification (CLH) as Repr. 1B.

In that context, it should be examined in more detail the possibility of proposing harmonised classification for all the group members where there is sufficient data to prepare a CLH dossier (e.g. as already done for 3-MP) or assess where read-across might be possible to use.

CLH i) will trigger company level risk management measures (RMM) under occupational safety and health (OSH) legislation for workers, ii) is needed or highly recommended for further regulatory processes under REACH and iii) is a prerequisite to restrict the presence of the substances in consumer mixtures, by means of the restriction entry 30 of REACH Annex XVII.

Professional use is typically widespread (at many sites and many users) with relatively low levels of operational controls and risk management measures but with typically frequent exposures with a long duration. In addition, professional users may be self-employed and therefore not covered by Occupational Health and Safety (OSH) legislation. Consumers may be co-exposed to the substances used by professionals. Therefore, a restriction of the substance as such or in mixtures (concentration limit in mixtures) used by professionals is suggested after CLH. Restriction of professional uses is preferred over authorisation as it is considered to be more efficient and effective to introduce controls at the level of placing on the market rather than at the level of uses.

In addition, the use of the most harmful substances by professional workers has been recognised as an area of concern under the European Commission’s Chemicals Strategy for Sustainability which aims to extend to professional users under REACH the level of protection granted to consumers.

As part of the restriction preparatory work, the added value of clarifying the ED properties in addition to the reproductive toxicity and P/vP and mobility properties should be considered.

C-alkylated pyrazoles that are not currently used in fertilisers but that could be used as alternatives in fertilisers (based on their potential for nitrification inhibition) and that have similar human health (reproductive toxicity and ED) and environment (P/vP and mobility) hazard properties should also be considered for further EU regulatory risk management. The above conclusion is relevant for the following members of the group: Pz (EC 206-017-1), 4-MP (EC 231-445-0). Similarly, the conclusion is relevant for 3,5-DMP (EC 200-657-5) even though it does not have the same human health hazard profile (no ED properties).

Based on currently available information, there is no need for EU regulatory risk management of the substances ECs 600-813-6, 689-662-5 and 823-314-7 in the sub-group 2 (N-alkylated pyrazoles).

Substances are registered only as intermediates, i.e. the N-alkylated pyrazoles (subgroup 2): 1,4-DMP (EC 600-813-6), 1,3-DMP (EC 689-662-5), 1-iPP (EC 823-314-7). In most cases, there is not enough hazard information to conclude on their potential hazard. In the absence of data and considering structural similarity to the C-alkylated pyrazoles, reproductive toxic potential can be assumed unless otherwise proven. Therefore, substances in the group could be very persistent and very mobile and/or persistent, mobile and toxic. The substitution potential of these substances for use in the fertilisers' sector is uncertain. For now, there is no need for further EU RRM on these substances.

However, it may be worth examining further the potential for substitution of substances in sub-group 2 (N-alkylated pyrazoles) as well as their hazard profile and, if relevant, include them in the restriction.

3 Conclusions and actions

The conclusions and actions proposed in the table below are based on the REACH and CLP information available at the time of the assessment by ECHA. The main source of information is the registration dossiers. Relevant public assessments may also be considered. When new information (e.g. on hazards through evaluation processes, or on uses) will become available, the document will be updated and conclusions and actions revisited.

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
Subgroup 1: C-alkylated pyrazoles					
215-925-7 3-methylpyrazole (3-MP) EC 424-640-9 1H-Pyrazole, 3,4-dimethyl-, phosphate (1:1)	Known or potential hazard for reproductive toxicity and ED	Known or potential hazard for P/vP and mobility	Use in fertilisers by professionals and consumers with potential for exposure.	**Need for EU RRM: Restriction** <u>Justification</u>: Restriction of the substances for the use in fertilisers due to Reproductive toxicity, potential ED and P/vP and mobility properties. The harmonised classification as Repr. 1B would trigger the restriction entry 30 and by that ensure that the substances are not included in consumer mixtures above the limits	**First step:** CCH **Next steps (if hazard confirmed):** CLH Restriction

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
				specified in that entry. Professional use is typically widespread (at many sites and many users) with relatively low levels of operational controls and risk management measures but with typically frequent exposures with a long duration. Restriction of professional uses is preferred over authorisation as it is considered to be more efficient and effective to introduce controls at the level of placing on the market rather than at the level of uses. The fertilisers regulation (EU 2019/1009) does not contain a specific clause that would prevent the use of	

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
				such hazardous substances in fertilisers and it states that the safety of its constituent substances for use in fertilisers should be established through REACH registration.	
200-657-5 3,5-dimethylpyrazole (3,5-DMP)	Known or potential hazard for reproductive toxicity	Known or potential hazard for P/vP and mobility	Professional use in coatings needs confirmation.	**Need for EU RRM: Restriction** <u>Justification</u>: Restriction of the substances for the use in fertilisers due to reproductive toxicity, potential ED and P/vP and mobility properties. The substances are not currently used in fertilisers. However, based on their potential for nitrification inhibition, they could be potential alternative.	**First step:** CCH **Next steps (if hazard confirmed):** CLH Restriction

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
206-017-1 Pyrazole (Pz) 231-445-0 4-methylpyrazole (4-MP) 429-130-1 3,4-dimethyl-1H-pyrazole (3,4-DMP)	Known or potential hazard for reproductive toxicity and ED	Known or potential hazard for P/vP and mobility	Industrial uses in pharmaceutical and electronic industry (EC 231-445-0).	**Need for EU RRM: Restriction** <u>Justification</u>: Restriction of the substances for the use in fertilisers due to reproductive toxicity, potential ED and P/vP and mobility properties. The substances are not currently used in fertilisers. However, based on their potential for nitrification inhibition, they could be potential alternative.	CLH Restriction
Subgroup 2: N-alkylated pyrazoles					
600-813-6 1H-Pyrazole, 1,4-dimethyl- (1,4-DMP) 689-662-5 1,3-dimethyl-1H-pyrazole (1,3-DMP)	Inconclusive hazard for HH	Known or potential hazard for P/vP and mobility (1,4-DMP). No data for 1,3-DMP and 1-iPP	The substances are only registered as intermediates.	**Currently no need for EU RRM** <u>Justification:</u> Currently no need for EU regulatory risk management as the substances are only	No action

Subgroup name, EC number, substance name	Human Health Hazard	Environmental Hazard	Relevant use(s) & exposure potential	Last foreseen action	Action
823-314-7 1-isopropyl-1H-pyrazole (1-iPP)				registered as intermediates. If any of such N-alkylated pyrazoles would be considered as substitute for some of the pyrazoles in subgroup 1 in their use as additives in fertilisers, appropriate REACH registrations with submission of data to fulfil the information requirements would be required by registrants. To be considered if relevant to include in the restriction proposed for subgroup 1.	

Annex 1: Harmonised classifications and self-classifications reported by registrants

Data extracted on 14 November 2019 (except EC 215-925-7: 29 October 2021)

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations	Classification in C&L notifications
Sub group 1: C-alkylated pyrazoles					
200-657-5	67-51-6	3,5-dimethyl-pyrazole		Acute Tox 4 (oral) H302 Repr. 2 f, d H361 STOT RE 2 (liver) H373	Skin Irrit. 2 H315 Eye Irrit. 2 H319 STOT SE 3 H335
206-017-1	288-13-1	pyrazole		Acute Tox 4 (oral) H302 Acute Tox 3 (skin) H311 Skin Irrit. 2 H315 Eye Dam. 1 H318 STOT RE 1 (thyroid, liver, spleen) H372 Aquatic Chronic 3 H412	STOT SE3 H335
215-925-7	1453-58-3	3-methyl-pyrazole	Repro 1B H360D	Acute Tox 4 (oral) H302 Eye Dam. 1 H318 Skin Corr. 1B H314 Repr. 2 f, d H361	Skin Irrit. 2 H315 Eye Irrit. 2 H319 STOT SE 3 H335
231-445-0	7554-65-6	4-methyl-pyrazole		Acute Tox 4 (oral) H302 Acute Tox 4 (skin) H312 Skin Corr 1C H314 Eye damage 1 H318	Skin Irrit. 2 H315 Eye Irrit. 2 H319 STOT SE 3 H335
424-640-9	20284 2-98-6	1H-Pyrazole, 3,4-dimethyl-, phosphate (1:1)		Acute Tox. 4 H302 Eye Irrit. 2 H319 Repr. 2 f, d H361 STOT RE 2 H373 (Liver, Kidney, ...)	
429-130-1	2820-37-3	3,4-dimethyl-	Acute Tox 4 (oral) H302 Eye damage 1		Repr. 2 f, d H361

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations	Classification in C&L notifications
		1H-pyrazole	H318 Aquatic Chronic 3 H412		
Sub group 2: N-alkylated pyrazoles					
600-813-6	1072-68-0	1H-pyrazole-1,4-dimethyl		Flam. Liq. 3 H226 Acute Tox. 3 H301 Acute Tox. 3 H311 Acute Tox. 3 H331 Eye Dam. 1 H318 STOT SE1 H370	Eye Irrit. 2A H319 Skin Irrit. 2 H315
689-662-5	694-48-4	1,3-dimethyl-1H-pyrazole		Flam. Liq. 3 H226 Skin Irrit. 2 H315 Eye Irrit. 2 H319 STOT SE 3 H335	Eye Irrit. 2A H319
823-314-7	18952-87-9	1-isopropyl-1H-pyrazole		Aquatic Chronic 2 H411	Flam. Liq. 3 H226 Skin Irrit. 2 H315 Eye Irrit. 2 H319

Annex 2: Overview of uses based on information available in registration dossiers

Data extracted on 14 November 2019.

Main types of applications structured by product or article types	EC/ List 200-657-5	EC/ List 206-017-1	EC/ List 215-925-7	EC/ List 231-445-0	EC/ List 424-640-9	EC/ List 429-130-1	EC/ List 600-813-6	EC/ List 689-662-5	EC/ List 823-314-7
Use in polymers prod. & modif.	F, I								
Use in fertilisers			F, P		F, I, P, C				
Use in manuf. of API (pharma)		I							
Use in electronics for wafer cleaning		I							
Use in coatings	I, P*								
Intermediate use	I			I			I	I	I

F: formulation, I: industrial use, P: professional use, C: consumer use, A: article service life; P, C and A are highlighted in red to indicate widespread use with potential for exposure/release

* Some of the registered uses may have been reported wrongly e.g. 3,5-DMP (EC 200-657-5), professional use in coatings. These could be clarified during further scrutiny.

Annex 3: Overview of completed or ongoing regulatory risk management activities

Data extracted in November 2019

EC/List number	RMOA	Authorisation		Restriction*	CLH	Actions not under REACH/ CLP
		Candidate list	Annex XIV	Annex XVII	Annex VI (CLP)	
Sub group 1: C-alkylated pyrazoles						
215-925-7					yes	
429-130-1					yes	

*Some of the broad restriction entries in the Annex XVII of REACH are not represented in the overview, e.g. when the scope of the restriction is defined by its classification or the substance identification is broad (e.g. entries 3, 28-30 and 40).

There are no relevant completed or ongoing regulatory risk management activities for the other substances.