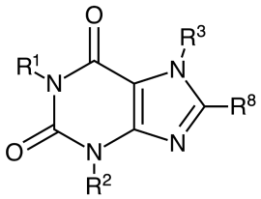
Assessment of regulatory needs

Authority: European Chemicals Agency (ECHA)

Date: 02 June 2020

Group Name: Dihydropurinedione derivatives

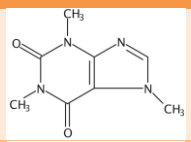
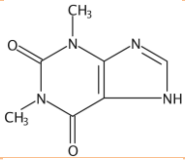
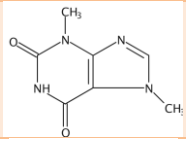
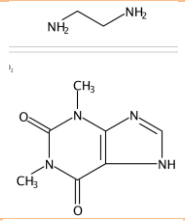
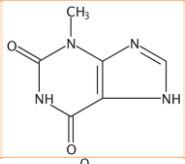
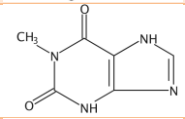
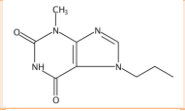
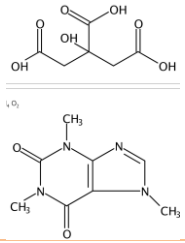
General structure:



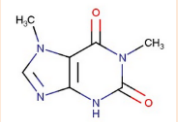
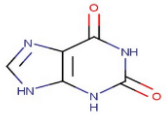
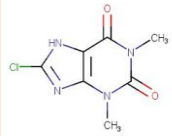
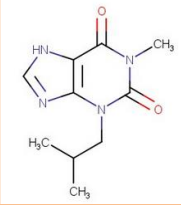
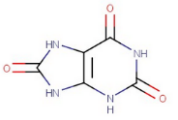
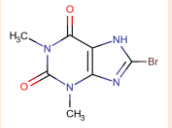
Revision history

Version	*Date*	*Description*
1.0	02 June 2020	

List of substances covered by the group

EC/List number	CAS number	Substance name/Substance name acronyms	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
200-362-1	58-08-2	caffeine		Full, 100-1000
200-385-7	58-55-9	theophylline		Full, 1-10
201-494-2	83-67-0	theobromine		Full, 1-10
206-264-5	317-34-0	aminophylline		C&L Notified
214-058-1	1076-22-8	3,7-dihydro-3-methyl-1H-purine-2,6-dione		OSII or TII
228-108-5	6136-37-4	3,7-dihydro-1-methyl-1H-purine-2,6-dione		C&L Notified
611-243-2	55242-64-3	1H-Purine-2,6-dione, 3,7-dihydro-3-methyl-7-propyl-		OSII or TII
614-938-9	69-22-7	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, mixt. with 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione		C&L Notified

[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

EC/List number	CAS number	Substance name/Substance name acronyms	Chemical structures	Registration type (full, OSII or TII, NONS), highest tonnage band among all the registrations (t/y) [1]
210-271-9	611-59-6	3,7-dihydro-1,7-dimethyl-1H-purine-2,6-dione (paraxanthine)		C&L Notified
200-718-6	69-89-6	purine-2(3H),6(1H)-dione (xanthine)		C&L Notified
201-590-4	85-18-7	8-chlorotheophylline		OSII or TII
207-526-1	479-18-5	diprophylline		C&L Notified
249-259-3	28822-58-4	3,7-dihydro-3-isobutyl-1-methyl-1H-purine-2,6-dione (isobutylmethylxanthine, IBMX)		C&L Notified
200-720-7	69-93-2	Uric acid		Full, 1-10
233-846-6	10381-75-6	8-Bromotheophylline		Pre-registered

This table contains also group members that are only notified under the CLP Regulation. However, the list is currently non-exhaustive. Should further regulatory risk management action on one or more substances in the group be considered, ECHA will make an additional search for related C&L notified substances to be included in the group and develop an assessment of regulatory needs for them.

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. An assessment 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 (or single substance) is to help authorities decide the most appropriate way to address the identified concern 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.

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

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 need for regulatory action can be identified for the whole group, a subgroup or for single substance(s). This will result in single or group entry in the Assessment for regulatory needs list of substances.

The assessment of regulatory needs is preferably done at an early stage, for instance, when an authority initiates work on a group of substances. It 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. 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 other EU legislation, or be generated in some cases. Uncertainties associated to the level of information used should be reflected in the documentation. A Member State or ECHA can carry out this case-by-case analysis. It can and should 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. Any authority can consequently initiate a regulatory process and should indicate this by appropriate means, such as the Registry of Intentions.

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

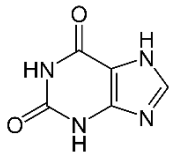
[2] https://echa.europa.eu/understanding-assessment-regulatory-needs

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
OSII 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
SVHC	Substance of very high concern

1. Overview of the group

ECHA has grouped together structurally similar substances based on the presence of the xanthine moiety shown in the figure below.



The group "Dihydropurinedione derivatives" consists of 15 members. The registered substances are well-defined di-hydro-purine-di-one (or *xanthine*) derivatives consisting of one multi-constituent and seven mono-constituent substances. Seven are notified to the C&L inventory (not registered) and one is pre-registered.

Xanthine derivatives are found in common food products and beverages such as cocoa, tea, coffee and as active ingredients in pharmaceuticals and cosmetics.

Regarding past or ongoing regulatory risk management activities, the Netherlands submitted a proposal for harmonised classification and labelling for theophylline (EC 200-385-7) as "Repr. 1B, H360D" (see also Annex 3).

Based on information reported in the REACH registration dossiers, only caffeine has widespread uses including uses in cosmetics that would result in potential for exposure.

The other substances of the group have either only industrial uses (mainly as intermediates or laboratory reagents), are transported intermediates with low potential for exposure or are only notified to the C&L inventory. Information from the Cosing Database (European Commission Inventory of Cosmetic ingredients) indicate that theophylline, theobromine and caffeine are used in cosmetics (skin conditioning function) however such use is not reported in the REACH registration dossiers.

The substances in the group are also used in pharmaceutical applications in humans and veterinary medicine (i.e. theophylline and aminophylline for the treatment of asthma and breathing difficulties).

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 no need for regulatory risk management action at EU level

Based on currently available information, there is no need for (further) EU regulatory risk management for all the group members.

The available information indicates that the substances in the group present no or unlikely hazard for the environment. The available biodegradation screening studies show very fast degradation under test conditions (caffeine, theophylline and theobromine). The octanol/water partitioning coefficients for the substances are around or below zero indicating no bioaccumulation potential. The substances are therefore considered likely not PBT or vPvB. There are indications from acute studies provided in the registration dossiers that these substances have limited effects to aquatic life showing ED50 values for daphnia and fish at or above 100 mg/l.

The substances in the group (methylxanthines) have the potential for reproductive toxicity (developmental toxicity). This is based on findings in experimental animal studies with caffeine, theobromine and theophylline and is extrapolated based on structural similarity to all the substances in the group. The potential for developmental toxicity applies to all methylated xanthines although some different potencies might be expected (theobromine is less biologically active compared to caffeine regarding receptor affinity binding). The property might not be relevant for xanthine and uric acid (non-methylated derivatives), however there is no information to support excluding them from this hazard potential.

A proposal for harmonised classification and labelling (CLH) for Theophylline is ongoing for reproductive toxicity (development). No further EU RRM is currently

needed. The only registered uses of theophylline are as intermediates and therefore a harmonised classification as reproductive toxicity cat. 1B should trigger sufficient risk management measures at company level according to workplace legislation to address workers safety. For potential uses in cosmetics (not reported in registration dossiers), the classification is sufficient to trigger - if needed - regulatory action under the Cosmetics Regulation. Under the Cosmetics Regulation, the use of substances classified as CMR 1A or 1B is prohibited.

For caffeine and theobromine that also have potential for reproductive toxicity, the available data and information from human intake and available threshold values set by regulatory authorities (i.e. caffeine and theobromine) do not justify further regulatory risk management, including CLH, as the reproductive effects are seen at very high exposure levels that do not occur in real life exposure situations[3]. In addition, theobromine is only registered for intermediate uses and the registrations do not report uses of caffeine and theobromine in cosmetic products (information from the Cosing database indicates uses of caffeine and theobromine in cosmetic products).

Aminophylline is a mixture containing theophylline and ethylenediamine (2:1 ratio). Ethylenediamine has a harmonised classification for skin and respiratory sensitisation and is included in the Candidate List. However, there is no need for further EU regulatory risk management for aminophylline as it is not registered under REACH[4].

For the remaining registered substances, the exposure potential is assumed to be low; taken together with the considerations for caffeine and theobromine no regulatory action under REACH (including data generation) is currently considered needed.

[3] The maximum amount of caffeine in cosmetic products is 5% which is lower than the amount of caffeine ingested with beverages. 11% of a dose of caffeine is converted to theobromine after ingestion (EFSA, 2017). Theobromine ingestion from all sources in humans can reach up to 7.1 mg/kg bw/day whereas for caffeine the estimation is up to 10mg/kg bw/day (EFSA, 2017). These amounts are higher than the values were reproductive toxicity has been observed in experimental animals with caffeine and theobromine.

[4] It is used in pharmaceuticals and thus subject to Directive 2001/83/EC and in Regulation (EC) No 726/2004.

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
All Dihydropurinedione derivatives **(except for those listed below)**	Known or potential hazard for reproductive toxicity	No hazard or unlikely hazard	Intermediate uses or only notified with low potential for exposure.	**Currently no need for EU RRM** Justification: The human health hazards are likely at very high exposure levels (extrapolating from caffeine). There is low exposure potential from uses.	No action
200-362-1 (Caffeine) **201-494-2 (Theobromine)**	Known or potential hazard for reproductive toxicity	No hazard or unlikely hazard	Consumer uses (e.g. cosmetics, fragrances) with high exposure potential.	**Currently no need for EU RRM** Justification: Human health hazards are likely to occur only at very high exposure levels that are much above	No action

				exposure levels for humans or the environment from the use of the substance.	
200-385-7 **(theophylline)**	Known or potential hazard for reproductive toxicity	No hazard or unlikely hazard	Industrial uses as intermediate with low exposure potential. Potential uses in cosmetics (not reported in registration dossiers)	**Currently no need for EU RRM** <u>Justification:</u> the substance is mainly used as intermediate. Harmonised CLH should be sufficient to ensure safe use by workers at industrial settings. In addition, the harmonised classification would support action under the Cosmetics Regulation.	No action CLH ongoing (for repro 1B)

Annex 1: Harmonised and self-classification

Data extracted on 2 June 2020

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations	Classification in C&L notifications
200-362-1	58-08-2	caffeine	-	Acute Tox. 4	-
200-385-7	58-55-9	theophylline		Acute Tox. 3	Acute Tox. 4
201-494-2	83-67-0	theobromine	-	Acute Tox. 4, Eye Irrit. 2	Carc. 2
206-264-5	317-34-0	aminophylline	-	-	Acute Tox. 3 (&4, Skin Sens 1, STOT RE1/SE1, eye dam 1, R 2, Lact.)
214-058-1	1076-22-8	3,7-dihydro-3-methyl-1H-purine-2,6-dione	-	Acute Tox. 4	Stot RE 2
228-108-5	6136-37-4	3,7-dihydro-1-methyl-1H-purine-2,6-dione	-	-	Skin irr. 2, eye irr. 2A, STOT SE 3
611-243-2	55242-64-3	1H-Purine-2,6-dione, 3,7-dihydro-3-methyl-7-propyl	-	Acute Tox. 4	-
614-938-9	69-22-7	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, mixt. with 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione	-	-	Acute Tox. 4, Eye Irrit. 2
210-271-9	611-59-6	paraxanthine	-	-	Acute Tox. 4
200-718-6	69-89-6	xanthine	-	-	Acute Tox. 4; Skin Sens. 1; Eye Irrit. 2
201-590-4	85-18-7	8-chlorotheophylline	-	Acute Tox. 4	Acute Tox. 4

EC/ List No	CAS No	Substance name	Harmonised classification	Classification in registrations	Classification in C&L notifications
207-526-1	479-18-5	diprophylline	-	-	Acute Tox. 4
249-259-3	28822-58-4	isobutylmethylxanthine	-	-	Acute Tox. 4
200-720-7	69-93-2	uric acid	-	-	Skin Irrit. 2; Eye Irrit. 2A ; STOT SE 3
233-846-6	10381-75-6	8-bromotheophylline	--	-	-

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

Data extracted on 2 June 2020

Main applications by product or article	EC/List 200-362-1	EC/List 200-385-7	EC/List 201-494-2	EC/List 214-058-1	EC/List 611-243-2	EC/List 201-590-4	EC/List 200-720-7
fragrances	F, I, **P, C**	-	-		-	-	-
cosmetics	F, I, **P, C**	-	-	-	-	-	C
intermediate	I	I	I	I	I	I	I
pharmaceuticals						**P**	

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

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

Data consulted on 5 March 2020

EC entries	RMOA	Authorisation		Restriction	CLH	Actions not under REACH/ CLP
		Candidate list	Annex XIV	Annex XVII	Annex VI (CLP)	
200-362-1	-	-	-	-	-	-
200-385-7	-	-	-	-	Repro. 1B(d) (NL)	-
201-494-2	-	-	-	-	-	-
214-058-1	-	-	-	-	-	-
611-243-2	-	-	-	-	-	-
201-590-4	-	-	-	-	-	
200-720-7	-	-	-	-	-	