Agency technical report on the classification and labelling of:

2-amino-2-methylpropanol

EC Number: 204-709-8
CAS Number: 124-68-5

July 2026

Contents

Brief summary

The conclusion of the Agency technical report is that 2-amino-2-methylpropanol meets the classification criteria for:

Skin Corr. 1; H314 (Causes severe skin burns and eye damage), with SCLs:

Skin Corr. 1; H314: C ≥ 35%

Skin Irrit. 2; H315: 5% < C < 35%

Eye Dam. 1; H318 (Causes serious eye damage)

STOT RE 2; H373 (May cause damage to the liver through prolonged or repeated exposure)

Repr. 1B; H360D (May damage the unborn child)

Is this in agreement with the RAC opinion? YES

At the time of publication, this mandatory classification and labelling (MCL) has not been agreed and/or adopted in Great Britain.

This is a targeted technical report which only considers skin corrosion/irritation, serious eye damage/eye irritation, reproductive toxicity, specific target organ toxicity – repeated exposure and environmental hazards. These were the only hazard classes considered in the EU Committee for Risk Assessment (RAC) Opinion.

Introduction

Under Article 37 of the GB CLP Regulation[1], the Agency[2] is required to produce a technical report for each substance on which the Committee for Risk Assessment (RAC) of the European Chemicals Agency produces an opinion[3].

This technical report documents an independent scientific assessment, conducted by HSE technical specialists with support from the Environment Agency for the environmental hazard classification, of the classification and labelling of 2-amino-2-methylpropanol.

Table 1. Information considered in the scientific assessment

Document	**Included in assessment**
EU CLH report	Yes
Annexes to the EU CLH report	Not applicable
RAC opinion	Yes
Background document	Yes
Information submitted during the EU public consultation process (RCOM table, including attachments)	Yes
RAC minority opinion(s)	Not applicable
Other information:	No

This information has been evaluated against the classification and labelling criteria set out in the GB CLP Regulation.

[1]The retained CLP Regulation (EU) No. 1272/2008 as amended for Great Britain

[2] HSE acting in its capacity as the GB CLP Agency

[3] Under Article 37(4) of Regulation (EU) No 1272/2008 on classification, labelling and packaging of substances and mixtures

Overview of current and proposed classification and labelling

Table 2. Current and proposed classification and labelling

	Index No.	International Chemical Identification	EC No.	CAS No.	Classification		Labelling			Specific Concentration Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard Statement Code(s)	Suppl. Hazard Statement Code(s)		
GB MCL List entry	603-070-00-6	2-amino-2-methylpropanol	204-709-8	124-68-5	Eye Irrit. 2 Skin Irrit. 2 Aquatic Chronic 3	H319 H315 H412	GHS07 Wng	H319 H315 H412			
EU dossier submitter's proposal	603-070-00-6	2-amino-2-methylpropanol	204-709-8	124-68-5	**Add** Repr. 1B STOT RE 2 **Modify** Skin Corr. 1 Eye Dam. 1 **Remove** Aquatic Chronic 3	**Add** H360D H373 (liver) **Modify** H314 H318 **Remove** H314	**Add** GHS08 **Modify** GHS05 Dgr **Remove** GHS07	**Add** H360D H373 (liver) **Modify** H314 **Remove** H412			
EU RAC opinion	603-070-00-6	2-amino-2-methylpropanol	204-709-8	124-68-5	**Add** Repr. 1B STOT RE 2 **Modify** Skin Corr. 1 Eye Dam. 1 **Remove** Aquatic Chronic 3	**Add** H360D H373 (liver) **Modify** H314 H318 **Remove** H314	**Add** GHS08 **Modify** GHS05 Dgr **Remove** GHS07	**Add** H360D H373 (liver) **Modify** H314 **Remove** H412		**Add** Skin Corr. 1; H314: C ≥ 35% Skin Irrit. 2; H315: 5% < C < 35%	
Agency technical report conclusion	603-070-00-6	2-amino-2-methylpropanol	204-709-8	124-68-5	**Add** Repr. 1B STOT RE 2 **Modify** Skin Corr. 1 Eye Dam. 1	**Add** H360D H373 (liver) **Modify** H314 H318	**Add** GHS08 **Modify** GHS05 Dgr	**Add** H360D H373 (liver) **Modify** H314		**Add** Skin Corr. 1; H314: C ≥ 35%	

	Index No.	International Chemical Identification	EC No.	CAS No.	Classification		Labelling			Specific Concentration Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard Statement Code(s)	Suppl. Hazard Statement Code(s)		
					Remove Aquatic Chronic 3	**Remove** H314	**Remove** GHS07	**Remove** H412		Skin Irrit. 2; H315: 5% < C < 35%	
Resulting MCL entry on GB MCL list	603-070-00-6	2-amino-2-methylpropanol	204-709-8	124-68-5	Repr. 1B STOT RE 2 Skin Corr. 1 Eye Dam. 1	H360D H373 (liver) H314 H318	GHS08 GHS05 Dgr	H360D H373 (liver) H314		**Add** Skin Corr. 1; H314: C ≥ 35% Skin Irrit. 2; H315: 5% < C < 35%	

Background

Active substance in Plant Protection Products: ☐

Active substance in Biocidal Products: ☐

Chemical registered under REACH: ☒

2-amino-2-methylpropan-1-ol (also known as -propanol, 2-amino-2-methyl- 2-azanyl-2-methyl-propan-1-ol; hereafter referred to as AMP) is an industrial chemical that functions as a pH stabiliser with anticorrosive properties used in a variety of applications, including washing and cleaning products, coating products, plant protection products, cosmetics and personal care products, lubricants and greases, biocides (e.g. disinfectants, pest control products) and perfumes and fragrances (CLH, 2024).

The structural formula of AMP is shown in Figure 1.

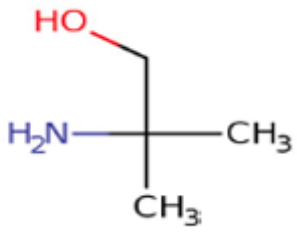

Figure 1: structural formula of AMP, taken from page 4 of the RAC opinion (ECHA, 2026)

In their assessment, RAC included studies using different grades of AMP (e.g. AMP-95, AMP-Regular, AMP Ultra) and 2-amino-2-methyl-1-propanol hydrochloride (AMP-HCl). Older studies used commercial grade AMP, which included undefined amounts of 2-methylamino-2-methyl-1-propanol (MMAMP) as an impurity. A summary of the pH levels of each type of AMP is provided in Table 3.

Table 3: pH of AMP, taken from page 4 of the RAC opinion (ECHA, 2026)

AMP quality	0.0001 % (w/w)	0.001 % (w/w)	0.01 % (w/w)	0.1 % (w/w)	1 % (w/w)	10 % (w/w)	100% (as received)
AMP Ultra PC 2000	8.28	9.41	10.08	10.63	11.35	11.81	13.11
AMP-95 (industrial grade)	8.22	9.60	10.32	10.68	11.24	12.03	13.41
					1 vol%		**100 vol%**
AMP Ultra PC 1000: high-purity grade	-	-	-	-	11.25	-	12.2

As AMP is highly alkaline, some of the available reproductive and repeated dose toxicity studies used 2-amino-2-methyl-1-propanol hydrochloride (AMP-HCl) to reduce its pH and avoid irritation of the gastrointestinal tract. AMP-HCl (EC 221-713-5, CAS 3207-12-3) is the hydrochloride salt of AMP. Based on molecular weights (MW) of this equimolar salt, AMP-HCl (MW = 125.60) contains 71.0% AMP (MW = 89.14). Therefore AMP-HCl doses can be converted into AMP doses using a correction factor of x 0.71 (CLH, 2024).

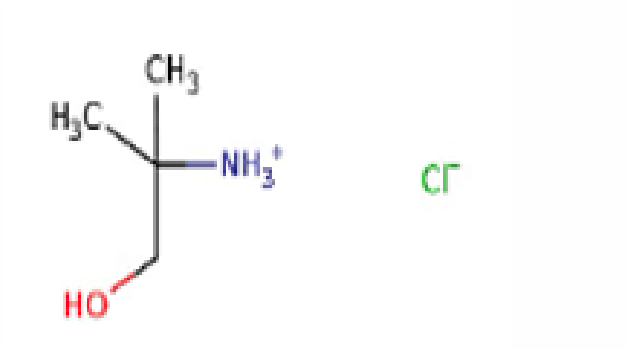

Figure 2: structural formula of AMP-HCl, taken from page 4 of the RAC opinion (ECHA, 2026).

The DS concluded that the use of studies with AMP-HCl was appropriate for the classification of AMP, referring to EU REACH Guidance R.7.6.2.3.2 (v6.0) (2017), which states '*It is to be noted that corrosive or highly irritating substances should be tested preferentially via the oral route, however it must be noted that in vivo testing with corrosive substances at concentration/dose levels causing corrosivity must be avoided (see REACH Annex VII-X preamble). The vehicle should be chosen to minimise gastrointestinal irritation*'.

RAC noted that AMP-HCl administered via the oral route is readily dissolved in gastrointestinal fluid and completely dissociates into a protonated amine form (AMP-H^+ cation) and a chloride ion. RAC considered that, after absorption into the bloodstream,

AMP-H^+ and the free base (AMP) are expected to be maintained in balance, based on the pH of blood (~7.4) being lower than the pKa of the compound (~9.69). RAC assumed that, in physiological blood, >99.5% of the compound would be present as AMP-H+, and < 0.5% present as AMP. As both forms remain in equilibrium, RAC concluded that the toxic effects of AMP-H+ and AMP would be similar. Overall, RAC concluded that the use of studies with AMP-HCl was appropriate for the assessment of reproductive toxicity and STOT RE for AMP.

The Agency agrees with this approach.

Scientific assessment of the physical, human health and environmental hazard classes

Physical Hazards

Not assessed in the CLH report or RAC opinion.

Health Hazards

Acute Toxicity

Not assessed in the CLH report or RAC opinion.

Specific target organ toxicity – single exposure (STOT SE)

Not assessed in the CLH report or RAC opinion.

Skin corrosion/irritation

Classification agreed by RAC:

AMP is an alkaline substance. High purity grade AMP has a pH of 12.2; the DS therefore suggested that the substance is expected to be corrosive.

Animal data

For the assessment of skin corrosion/irritation, no OECD test guideline (TG) or GLP-compliant studies were available and all available studies were conducted before GLP was in place. Therefore all *in vivo* studies had limited reporting, missing information on scoring or non-standard exposure duration or observation periods.

An *in vivo* study on rabbits was available (Anonymous, 1940). There was no information regarding the strain of rabbits or the number used. Rabbits were exposed to one of the following:

1. Neat AMP at a dose of 10g/kg (no vehicle) rubbed onto the skin in a solid state
2. A solution of 10% AMP suspended in glycerol
3. A solution of 25% AMP dissolved in water. This required neutralisation with hydrochloric acid (HCl).

Rabbits were exposed daily for 5 days. The substance was applied to clipped skin on the abdomen and treated areas were left completely uncovered. In all exposure groups, treatment sites were washed with soap and water after 4 hours of contact.

In group 1, no evidence of injury to the skin was noted during treatment or in a subsequent observation period (duration unspecified). No changes in body weight were observed.

In groups 2 and 3, there were no signs of skin irritation. Body weight loss was noted, which was characterised as ‘slight’ by the study author, but no further information regarding the magnitude of this finding was available. Body weight loss was stated to have recovered during the observation period.

No grading of skin reactions was available. On this basis, combined with the poor reporting and deviation from the relevant OECD TG (404), RAC concluded that the study was inconclusive for the evaluation of skin corrosion/irritation.

In a rabbit corrosivity test described as being concurrent with US Department of Transportation (DOT) regulations, 6 albino rabbits were exposed to AMP-Regular or AMP-95 (Anonymous, 2001a; study conducted in 1975). A 0.5 ml dose of the test material was applied neat to the shaved backs of 6 rabbits using an occlusive method. After 4h patches were removed and sites were cleaned. Sites were evaluated immediately for erythema, oedema and tissue destruction. No corrosion was reported, though no further information regarding the grading of skin reactions was available. No data were available on skin reactions within the 14 days following exposure, and RAC therefore considered that the study was not adequate to evaluate skin corrosion/irritation.

An acute dermal toxicity test was also available, conducted in rabbits of unspecified strain (Anonymous 1980c). Groups of 4 rabbits /sex/dose (2 abraded, 2 unabraded) received dermal applications of AMP (P-1826) to shaved skin at doses of 1000, 1500 or 2000 mg/kg bw/d, followed by a 14-day observation period.

After removal of the patch, both the abraded and intact treatment sites were severely irritated and black in colour. The treated sites became necrotic within 2 – 3 days and remained necrotic for the whole 14 day observation period. Body weight loss was observed in all animals, although no information regarding the magnitude or incidence of this effect was available. No other signs of toxicity were documented. RAC noted that the exposure duration used in this study was 24 hours; this was much longer than the duration recommended in OECD TG 404 for assessment of acute dermal irritation/corrosion. Therefore, RAC concluded that this study was not suitable for the evaluation of skin corrosion/irritation.

A short study summary was also available, though only very limited study details were included (Anonymous 1976a). A group of 6 rabbits were administered undiluted AMP (P-1826). Dose levels, animal strain and sex were not specified. The study authors reported

that AMP was a severe skin irritant with an irritation index of 6.1 and was not corrosive. Although RAC considered this study to indicate that AMP may have irritative properties, they concluded that it was not possible to directly compare the results with the CLP classification criteria based on the lack of information provided.

Human data

Human data were available in the form of skin prick and patch tests, conducted to investigate two cases of airborne dermatitis in a cosmetic company after exposure to AMP-100 (Cipolla *et al.*, 1997). Both workers suffered from periorbital oedema and facial erythema, which improved during weekends and holidays. The study was conducted to determine whether the mechanism of dermatitis was skin irritation or skin sensitisation. Skin prick tests and patch tests were conducted with the two workers, plus an additional 8 (2 from the same production line, 6 from others). Each worker received applications of AMP dissolved in distilled water (0.1 %, 0.5%, 1 %, 2%, 5%, 10% and 20%;) and AMP dissolved in ethyl alcohol (0.1 %, 0.5%, 1 %, 2%, 5%, 10% and 20%). Patches were applied to the back for 48h, with readings taken shortly after patch removal and 24 hours later. Results were scored as follows: erythema (+), erythema plus oedema (+ +), erythema plus oedema plus blisters (+ + +).

Patch tests were negative at low concentrations but at 10% and 20% AMP in both vehicles (distilled water and ethyl alcohol) erythema and oedema were recorded in all investigated subjects (Table 4).

Table 4: patch testing for workers in different parts of the cosmetics company, high concentrations only in water and alcohol (taken from page 18 of the CLH report (CLH, 2024)).

Test substance	Subjects with symptoms		Same production line without symptoms		Different production lines, without symptoms					
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
AMP-100, 10% in water	+	+	++	+	+	+	++	+	+	+
AMP-100, 20% in water	++	++	++	+	++	++	+	+	+	+
AMP-100, 10% in ethyl alcohol	+	++	++	++	+	+	+	++	++	++
AMP-100, 20% in ethyl alcohol	++	++	++	++	++	++	++	++	+	++

Scoring: erythema (+), erythema plus oedema (+ +), erythema plus oedema plus blisters (+ + +).

The study authors concluded that the positive responses at 10% and 20% were signs of irritation. RAC agreed with this conclusion, but noted that the study did not test neat AMP and therefore could not be used to inform on the irritation potential of neat AMP or AMP as

placed on the market. They additionally noted that the exposure time (48 hours) was much longer than 4 hours and the time until reading of reactions was shorter than 14 days.

Comparison with the classification criteria

RAC concluded that, owing to significant deviations from OECD TGs and a lack of detailed reporting, the animal data were not suitable to evaluate AMP for skin corrosion/irritation. However, they noted that the acute dermal study (Anonymous, 1980c) demonstrated skin corrosion after 24 hrs of exposure to neat AMP, which later developed into necrosis. Irritation (erythema + oedema) was observed in human patch tests with 10% and 20% AMP in different media (Cipolla *et al*., 1997).

RAC referred to the following text in section 3.2.2.2.5 of Annex I to the CLP Regulation: '*Likewise, pH extremes like* $\leqslant$ *2 and* $\geqslant$ *11,5 may indicate the potential to cause skin effects, especially when associated with significant acid/alkaline reserve (buffering capacity). Generally, such substances are expected to produce significant effects on the skin. In the absence of any other information, a substance is considered as corrosive to skin (Skin Corrosion Category 1) if it has a pH* $\leqslant$ *2 or a pH* $\geqslant$ *11,5. However, if consideration of acid/ alkaline reserve suggests the substance may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated in vitro test*'.

This statement was supported by a study by Craan *et al*. (1997), which found alkaline reserve to have an influence on skin corrosive properties after correlating effects in humans after exposure to 23 household cleaning agents with pH and titratable acid/alkaline reserve (TAR). Craan *et al*. suggested the following criteria for determining corrosive/irritation potential:

- pH ≥ 13.0 → corrosive
- 10.5 ≤ pH < 13.0 and alkaline reserve > 5 (liquids) → corrosive
- 12.0 ≤ pH < 13.0 and alkaline reserve < 5 (liquids) → irritant
- 10.5 ≤ pH < 12.0 and 3 ≤ alkaline reserve < 5 (liquids) → irritant
- pH < 10.5 → no labelling required
- 10.5 ≤ pH < 12.0 and alkaline reserve < 3 (liquids) → no labelling required

High purity AMP (AMP Ultra PC 1000) and industrial AMP (AMP-95) have pH values of 12.2 and 13.41, respectively, thus meeting the criteria in section 3.2.2.2.5 of Annex I to the CLP Regulation for classification as corrosive. Information on the alkaline reserve of different solutions of AMP was not available in the CLH report but was provided to RAC by an industry representative. This information is summarised in Table 5.

Table 5: alkaline reserve of various aqueous solutions of AMP, taken from page 9 of the RAC opinion (ECHA, 2026)

Samples	Sample preparation			Results	
	Added AMP-95 (% weight)	**Added Water** (% weight)	**Resulting AMP concentration** (% weight)	**Measured pH**	**Alkali Reserve** (g NaOH/ 100 g)
AMP5	5.3	94.7	5	11.9	0.5
AMP10	10.5	89.5	10	11.9	1.2
AMP20	21.1	78.9	20	12.3	2.6
AMP30	31.6	68.4	30	12.4	4.8
AMP95	100.0	0.0	95	13.3	16.0

RAC noted that pH value and alkaline reserve may be combined for the purposes of skin corrosion classification, using the formula provided in section 3.2.3.2.1.1 of ECHA's Guidance on the Application of the CLP Criteria (ECHA, 2024b), where a corrosive classification is required if pH + 1/12 alkaline reserve ≥ 14.5. In the case of industrial AMP (AMP-95 in Table 5), this sum is 13.3 + 16.0/12 = 14.63, therefore indicating corrosivity.

Based on the considerations of pH and alkaline reserve, RAC concluded that AMP warranted classification as **Skin Corr. 1; H314 (Causes severe skin burns and eye damage)**.

Specific concentration limits (SCLs)

RAC concluded that AMP with high alkalinity and high alkaline reserve warranted classification as Skin Corr. 1. However, they noted that other forms of AMP placed on the market have lower pH values and alkaline reserves (see Table 5). Therefore, they considered that it may be appropriate to set SCLs for skin corrosion and irritation.

The generic concentration limit (GCL) for a Category 1 base with pH ≥ 11.5 is ≥ 1%. Applying this concentration limit would result in any mixture containing ≥ 1% AMP being classified as Skin. Corr. 1. However, application of the formulae for corrosive (pH + 1/12 alkaline reserve ≥ 14.5) and irritant (pH value + 1/6 alkaline reserve ≥ 13) classifications in section 3.2.3.2.1.1 of ECHA's Guidance on the Application of the CLP Criteria (ECHA, 2024b) and a study by Young *et al.* (1988), respectively, yielded 'non-irritant' classifications for solutions of up to 20% AMP (Table 6), whilst a solution of 30% AMP yielded an 'irritant' classification.

Table 6: Calculations of irritation/corrosion properties of AMP based on pH and alkaline reserve according to formulas given in the Guidance on the Application of the CLP Criteria and in a study of Young et al. (1988), taken from page 11 of the RAC opinion (ECHA, 2026).

Name of sample	Concentration of AMP in the sample	pH of the sample	Alkaline reserve of the sample	pH value + 1/12 alkaline reserve value to be ≥ 14.5	pH value + 1/6 alkaline reserve value to be ≥ 13	Classification according to Guideline
AMP 5	5%	11.9	0.5	11.94	11.98	Non-irritant
AMP 10	10%	11.9	1.2	12.0	12.1	Non-irritant
AMP 20	20%	12.3	2.6	12,52	12,73	Non-irritant
AMP 30	30%	12.4	4.8	12.8	**13.2**	**Irritant**
AMP 95	95%	13.3	16	**14,63**	**15.97**	**Corrosive**

RAC also compared the pH and alkaline reserve values in the table above to the criteria defined by Craan *et al*. (1997), described in the 'Comparison with the classification criteria' section above. Based on these criteria, AMP-95 would warrant classification as corrosive (pH ≥ 13.0), whereas AMP-20 and AMP-30 would warrant classification as irritant (12.0 ≤ pH < 13.0 and alkaline reserve < 5) and AMP-5 and AMP10 would not require labelling (10.5 ≤ pH < 12.0 and alkaline reserve < 3). Overall, RAC concluded that, according to criteria developed by Young *et al.* (1988) and Craan *et al*. (1997), solutions of 5% and 10% AMP should not be classified for skin irritation, thus questioning the relevance of the ≥1% Category 1 GCL for AMP.

No *in vitro* data were available to confirm the lack of corrosivity/irritation potential of lower concentrations of AMP, as recommended in section 3.2.2.2.5 of Annex I to the CLP Regulation. However, RAC referred to the results of the human clinical study by Cipolla *et al.*, 1997, which indicated that exposure to a solution of 10% AMP caused skin irritation, whilst no reactions were observed after exposure to 5% AMP. Whilst RAC did not consider the study by Cipolla *et al*. (1997) to be sufficient to classify AMP for skin corrosion/irritation, owing to the use of lower concentrations of the substance than those placed on the market, they concluded that it was reliable enough to set SCLs.

As discussed above, Cipolla *et al.* identified moderate positive skin reactions (irritation) after exposure to AMP in solutions of 10% and 20% (see Table 4), in the form of erythema and erythema + oedema. None of the test subjects exhibited extreme responses such as blistering, which would be expected after exposure to a strong acid/base. Taking these results into account, combined with the criteria defined by Young *et al*. (1988) and Craan *et al*. (1997), RAC concluded that concentrations of up to 5% AMP could be considered

non-irritant. On this basis, RAC proposed a Category 2 (skin irritation) SCL for AMP of > 5%.

None of the test concentrations used by Cipolla *et al*. (up to 20% AMP) caused skin corrosion. Therefore, it was not possible to set an SCL for Category 1 (skin corrosion) based on this study. Instead, RAC determined a Category 1 SCL using the available data on the pH and alkaline reserve of AMP.

RAC used measurements provided by industry to determine the relationship between the concentration of AMP and its pH and alkaline reserve, and compared this to the formulae defined in section 3.2.3.2.1.1 of ECHA's Guidance on the Application of the CLP Criteria (ECHA, 2024b) for skin corrosion (pH + 1/12 alkaline reserve ≥ 14.5) and Young *et al*. (1988) for skin irritation (pH value + 1/6 alkali reserve ≥ 13). The calculations for increasing concentrations of AMP are shown in Table 7.

Table 7: Calculations of irritation/corrosion properties of AMP based on pH and alkaline reserve, taken from page 15 of the RAC opinion (ECHA, 2026).

Concentration of AMP in the sample	pH of the sample	Alkaline reserve of the sample	pH value + 1/12 alkaline reserve value to be ≥ 14.5	pH value + 1/6 alkaline reserve value to be ≥ 13	Classification according to Guideline
30%	12.4	4.8	12.8	13.2	**Irritant**
35%	12.4	5.5	12.84	13.3	**Irritant**
40%	12.5	6.5	13.04	13.6	**Irritant**
50%	12.65	8.0	13.3	13.98	**Irritant**
60%	12.8	10.0	13.6	14.5	**Irritant**
70%	12.95	11.6	13.9	14,9	**Irritant**
75%	13.0	12.5	14.04	15.1	**Irritant**
80%	13.1	13.2	14.2	15.3	**Irritant**
86%	13.2	14.2	14.4	15.6	**Irritant**
90%	13.25	15.0	**14.5**	-	**Corrosive**
95%	13.3	16.0	**14.6**	-	**Corrosive**

The calculations in Table 7 indicate that, according to the formulae defined by section 3.2.3.2.1.1 of ECHA's Guidance on the Application of the CLP Criteria (ECHA, 2024b) and Young *et al*. (1988), concentrations of 90% and 95% AMP should be considered corrosive, whilst concentrations below this should be considered irritant. In contrast, comparison of the pH and alkaline reserves listed in Table 7 to the criteria set by Craan *et al*. (1997) would indicate that solutions of 35% AMP should be considered corrosive, based on 10.5

≤ pH < 13.0 and alkaline reserve > 5. Using the more conservative criteria defined by Craan *et al*., RAC concluded that a Category 1 SCL of ≥ 35% was appropriate for AMP.

Overall conclusion

Overall, RAC concluded that AMP warranted classification as **Skin Corr. 1; H314 (Causes severe skin burns and eye damage)**, with the following SCLs:

Skin Corr. 1; H314: C ≥ 35 %

Skin Irrit. 2; H315: 5 % < C < 35 %.

Classification proposed by the Agency:

The Agency agrees with RAC's conclusion on classification. AMP meets the criteria for classification as **Skin Corr. 1; H314 (Causes severe skin burns and eye damage)**, with the following SCLs:

Skin Corr. 1; H314: C ≥ 35 %

Skin Irrit. 2; H315: 5 % < C < 35 %.

Serious eye damage/irritation

Classification agreed by RAC:

AMP is an alkaline substance. High purity grade AMP has a pH of 12.2 and the DS therefore expected the substance to produce significant effects on eyes. Two consecutive non-guideline studies in rabbits were available, both using Draize scoring systems. Neither study was conducted according to OECD TGs or GLP.

In the first study, two groups of 6 rabbits (strain undetermined) were administered either AMP regular or AMP-95 directly into the eye (Anonymous, 1975b). The substance was not rinsed after application. Scoring after 24 and 48h resulted in maximum Draize scores of 110 for each animal. RAC noted that the study summary in the EU REACH registration dossier also stated that vision was destroyed in all animals.

In the second study, groups of 6 rabbits (strain undetermined) were administered 0.1 mL of AMP regular or AMP-95 (no details on purity) for a period of 15 or 30 seconds, before washing with distilled water. Draize scores were within the range between 68.6 and 89.3; the time of scoring is not reported. Reversibility of effects was not investigated.

Comparison with classification criteria

RAC referred to Section 3.3.2.2.4 of Annex I to the CLP Regulation, which states: '*pH extremes like ≤ 2 and ≥ 11,5 may produce serious eye damage, especially when associated with significant acid/alkaline reserve (buffering capacity). Generally such substances are expected to produce significant effects on the eyes. In the absence of any other information, a substance is considered to cause serious eye damage (Category 1) if it has a pH ≤ 2 or ≥ 11,5*'. With a pH pf 12.2, RAC noted that AMP met this criterion.

Administration of AMP to the eye gave high Draize scores in two non-guideline studies, with a maximum score of 110 without washing after application. RAC noted that, in this study, scoring was only done 24 and 48 hours after application, with no measurements of the reversibility of the effects. They highlighted that, according to the Draize scoring system (Draize, 1959 in ECHA, 2026), a score of 110 is indicative of >75% of the cornea being covered by maximal opacity, along with destructed iris with haemorrhages, red conjunctivae, swelling of lids and discharge around the eye.

The scores obtained in the studies by Anonymous, 1975a and 1975b could not be directly compared with the CLP classification criteria. However, RAC considered that the effects seen in these studies were similar to the Category 1 criteria given in Table 3.3.1 of Annex I to the CLP Regulation: *'(b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1,5; calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material'*. On this basis, combined with the high pH of AMP, RAC concluded that classification as **Eye Dam. 1; H318 (Causes serious eye damage)** was warranted.

Classification proposed by the Agency:

The Agency agrees with RAC's conclusion on classification. AMP meets the criteria for classification as **Eye Dam. 1, H318 (Causes serious eye damage)**.

Respiratory sensitisation

Not assessed in the CLH report or RAC opinion.

Skin sensitisation

Not assessed in the CLH report or RAC opinion.

Specific target organ toxicity – repeated exposure (STOT RE)

Classification agreed by RAC:

Human data were provided by the DS in the form of clinical studies on the pharmaceutical 'Pamabrom', an AMP salt of 8-bromotheophylline (equimolar mixture of 74.4% w/w 8-bromotheophylline (CAS No. 10381-75-6) and 25.6% w/w AMP). Pamabrom is used as a diuretic agent. A bioequivalence study (2019) stated that AMP from Pamabrom and AMP are expected to behave similarly. However, the clinical studies available to the DS suffered from several drawbacks and deviations, including uncertainty around exposure levels/duration and co-exposures. Therefore, the clinical studies on Pamabrom were not considered suitable to assess AMP-HCl_AMP and AMP-HCl for STOT RE, and RAC did not discuss them further.

RAC considered hepatotoxicity to be the leading health effect of AMP in animal studies. Several oral studies (rat, dog, rabbit, mouse, monkey) and one inhalation study (rat) were available. For dermal exposure results from an OECD TG 414 study in rats was available.

Rat studies

A 5-day non-guideline study in Long-Evans rats was available. Groups of 5 rats/sex/dose group were administered 0, 500, 1000 or 2500 mg/kg bw/d of AMP regular (industrial grade) at pH >11 by oral gavage. Administration was for 5 days total followed by a 10-day recovery period.

Mortalities occurred at the mid and top dose: 2/5 females at the mid dose (days 6 and 11). At the top dose, all animals died on day 2 or day 3.

A reduction in body weight gain was noted in males at the mid dose, which was not statistically significant; this was normalised during the recovery period. Stagnation was noted in females.

A 14-day range finding study (for an OECD TG 421 study) in rats was available. Groups of 5 (Crl:CD(SD)IG SBR) rats/sex/dose group were administered 0, 100, 300, 600 or 800 mg/kg bw/d of AMP-HCl via the diet.

Effects were seen in top dose animals only. A slight increase in liver weights in males was noted (absolute +12.3%, relative +12.2%). There were no other findings.

A prenatal developmental toxicity study was available, conducted in line with OECD TG 414. Groups of 25 female rats were administered AMP-95 (adjusted for pH 6.72-7.46 using 1N sodium hydroxide and/or hydrochloric acid) at 0, 30, 100, or 300 mg/kg by oral gavage over GD 6-20.

A statistically significant increase in liver weight was noted at the top dose (+14.3%).

Hepatocellular vacuolation was noted in mid and top dose animals with an incidence of 19/25 and 23/25 respectively. Focal necrosis was also noted in both groups, characterised as minimal and present in 3/25 and 2/25 at the mid and top doses respectively. At the top dose, minimal multifocal necrosis was also found in 1/25 animals.

No relevant macroscopic findings in dams were reported. One female of the high dose group and one female of the mid dose group had macroscopic findings of discoloured liver, described as pale/tan or tan, respectively. The discoloration correlated with mild hepatocellular vacuolation.

An Extended One Generation Reproductive Toxicity study – cohorts 1A and 1B without extension was available, which was GLP-compliant. Groups of 25 CD(SD) rats/sex/dose were administered 0, 50 and 100 mg/kg bw/d with a top dose group of 30 CD(SD) rats/sex administered a dose of 200 mg/kg bw/d AMP-HCl. Doses were equivalent to 0, 35, 71 and 142 mg/kg bw/d AMP and were administered via the dietary route.

In the F0 generation, one female at the low dose group was euthanised in extremis, with signs of toxicity including hunched posture, thin/pale body, red material around the nose, pale/cool extremities, uterine adhesion, 1 mummified foetus, 2 autolysed foetuses *in utero* and evidence of a uterine infection. Some sporadic signs of systemic toxicity were noted in this study, such as hunched posture, hair loss and scabbing, but these either did not show a dose-response relationship or occurred at a similar incidence to control animals.

Dose-related increases in liver weights were noted in F0 males (+1.3%, 3.3% and +11.6% at 50, 100 and 200 mg/kg bw/d respectively, compared to controls). This was accompanied by moderate hepatocellular vacuolation in 24/30 males. Kidney weight was statistically significantly increased in mid and top dose F0 males (+3.4%, +7.9% and +9.1%% at 50, 100 and 200 mg/kg bw/d respectively, compared to the controls).

Hepatocellular vacuolation was seen in mid and low dose animals, at incidences of 4/25 (minimal) and 11/25 (minimal to mild) at 50 and 100 mg/kg bw/d respectively.

In a reproductive/developmental toxicity screening test conducted in line with OECD TG 421 and GLP, groups of 12 CD rats/sex/group were administered AMP-HCl via the dietary route. Doses of AMP-HCl were 0, 100, 300 and 1000 mg/kg bw/d, equivalent to 0, 71, 213 and 710 mg AMP/kg bw/d. Females were dosed 2 weeks prior to mating, through the mating period, gestation and until PND 4 (total of 42-49 days), males were dosed 2 weeks prior to breeding, through breeding until necropsy (total of 38 days), pups were euthanised on PND 4.

At the top dose there was a statistically significant increase in absolute and relative liver and kidney weights in males. In the kidney, absolute weights increased by 16.6% and relative weights by 11.2%. In the kidney, absolute weights increased by 21.3% and relative weights by 15.8%.

Kidney weight changes were not associated with microscopic findings.

RAC described a very slight degree of microvacuolisation of periportal hepatocytes, with or without vacuolisation of hepatocytes consistent with fatty change in top dose animals. These findings were not associated with hepatocellular necrosis or death, and were interpreted by the study authors as reversible.

An 8-week non-guideline supporting study was available. Groups of 10 CD rats/sex/dose were administered AMP at levels of 100, 2000, 4000, 8000 or 16000 ppm via dietary route. Mean achieved doses were 78/89, 162/174, 314/345, 625/717 and 1359/1355 mg/kg bw/d.

There were 2 mortalities in top dose females. These animals also exhibited emaciation, rough hair coat and scattered lesions (1x1mm) over the dorsal surface.

Hepatocellular vacuolation was seen in all dose groups 1/2 males and 1/2 females (very sight to slight); 2/2 males and 0/2 females (very slight to moderate); 2/2 males and 1/2 females (very slight to moderate); 10/10 males and 7/10 females (very slight to moderate) and 10/10 males and 8/10 females (slight to moderate) at 78/89, 162/174, 314/345, 625/717 and 1359/1355 mg/kg bw/d respectively.

At the top dose, a decrease in body weight gain was noted (-16.3% in males and - 21.8% in females).

Alopecia occurred in 3 males and 6 females. Focal skin ulceration occurred in 3 males and 5 females. No information regarding the magnitude of these was available.

A non-guideline repeat dose toxicity test was available that was similar to OECD TG 408. It was not GLP-compliant. Groups of 20 SD rats/sex/dose group were administered AMP-95/HCl via the dietary route for 90-92 days. Dose levels were 0, 25, 150, 250 and 2500 ppm; equivalent to 1.9/2.2, 11/13, 19/23 and 187/233 mg APM/kg bw (M/F). Infection with Sialodacryoadenitis virus (SDAC) was reported during weeks 5 and 6, and the study authors considered this to have had an impact on the results of the study. Microscopic evaluations were only completed in top dose and control animals.

Mortalities were seen in multiple groups: 1 female in the control and 1 female at 23 mg/kg bw/d on day 38 and one top dose female on day 18. All 3 animals showed signs of food consumption, constipation, lethargy, and a swollen abdomen.

A statistically significant increase in relative kidney weights was noted in top dose males (+11.0%).

Statistically significant increases in absolute and relative spleen weights were noted in top dose females: ↑ 19.8% abs. ↑ 14.6% rel.

Lower total bilirubin was noted in males at 19 mg/kg bw/d and males and females in the top dose group. No details regarding the magnitude of the change were available.

Clinical chemistry showed an increase in SGOT and LDH activities in males and females. Higher alkaline phosphatase activities and lower total protein and globulin levels in females were reported. No details regarding the magnitude of these changes were available.

Another non-guideline 13-week supporting study was conducted in CD rats. Groups of 10/sex/dose group were administered AMP regular at levels of 0, 500, 750, 1100 and 1700 mg/kg bw/d by oral gavage. This was conducted without a pH adjustment (pH 11+) and with a pH adjustment using hydrochloric acid (pH 7).

At pH 11:

Mortalities were seen in all dose groups: 2/10 M and 0/10 F, 3/10 M and 4/10 F, 3/10 M and 8/10 F, and 10/10 M and 9/10 F at 500, 750, 1100, and 1700 mg/kg bw/d respectively. From 750 mg/kg bw/d, dosing caused abdominal swelling (always followed by death), nasal and mouth bleeding and loss of hair around the face.

Liver histopathology was only conducted on 1/80 treated rats due to high mortality rates. No effects were observed.

Reduced red blood cell count was noted in males in multiple groups (-6.3%, -14.8% and -19.8% in 500, 750 and 1100 mg/kg bw/d respectively). Haematology parameters were also reduced in males at 1100 mg/kg bw/d: -haematocrit -9%, haemoglobin -9.7%.

At pH 7:

Two animals died at the top dose (1 male in week 12, found to have haemorrhages in the lung, stomach hyperaemia and haemorrhages in the intestine, and 1 female in week 10, found with enlarged liver and enlarged, haemorrhagic cortex of the kidney). Clinical signs of systemic toxicity were seen in top dose animals only. These were hyperactivity and hyperirritability, loss of hair, skin ulceration.

Clinical chemistry findings included changes in SGPT values (+530% in males only at 1100 mg/kg bw/d; +176% in males and +62% in females 1700 mg/kg bw/d respectively). OCT values were also increased in males (+273% and +156% at 1100 and 1700 mg/kg bw/d respectively). At the top dose, total protein was reduced (-9.9% in males and -8% in females).

Mouse studies

In an 8-week non-guideline study, groups of 10 CD-1 mice/sex/dose group were administered AMP regular (P-1826) (no purity indicated, unclear identity, no info on pH adjustment) at doses of 0, 200, 400, 800, 1600 and 3200 ppm via the diet.

No effects were observed on body weight or food consumption. No effects were observed in gross pathology or liver histopathology.

Dog studies

In a 28-day range finding study, 1 beagle dog/sex/group was administered an indistinct form of AMP (described as P-1826, no purity indicated, unclear identity) at levels of 600, 1800, 5400 or 16200 ppm. Doses were equivalent to 20/19, 54/70, 62/183 and 80/108 mg AMP/kg bw/d via the dietary route.

Soft stools and/or diarrhoea were noted for both dogs at 54/70 mg/kg bw/d, the female at 62 mg/kg bw/d and both dogs in the top dose group. Dry nose and mouth were also reported at the top dose.

Absolute and relative liver weights were both decreased; relative liver weights by 20% in males and 13.3% in females; and 6.6% in males and 3.3% in females in the 62/183 and 80/108 mg AMP/kg bw/d groups respectively.

Histopathological studies found hepatocellular vacuolation in the top 3 dose groups: both animals in the 54/70 mg/kg bw/d group (very slight to slight), both animals in the 62/183 mg/kg bw/d group (slight to moderate) and both animals in the top dose group (moderate to marked). Fibroplasia was found in the same groups: in the male dog only (slight centrilobular) in the 54/70 mg/kg bw/d group; in the female dog only (slight centrilobular) in the 62/183 mg/kg bw/d group and in the male dog only (very slight centrilobular) in the top dose group. Liver cell necrosis was noted in both animals in the 54/70 mg/kg bw/d group (small foci, centrilobular) and in the male only in the top dose group (scattered foci).

Clinical chemistry findings were elevated AP and SGPT levels for all dogs at 1800, 5400 and 16200 ppm, some increase was also seen in SGOT activity in the two highest doses (compared to values before dosing).

A non-guideline supporting study (similar to OECD TG 409) was available. Groups of 4 beagle dogs/sex/dose group were administered AMP-95/HCl via the dietary route for 3 months. Dose levels were 0, 25, 600 and 2500 ppm, equivalent to 0.78/0.85, 17/17 and 81/81 mg AMP/kg bw/d (M/F).

There were no mortalities or clinical signs of systemic toxicity recorded.

A statistically significant decrease in haemoglobin concentration was found in top dose females (-16%).

Clinical chemistry showed increased SGOT (2-4 fold), SGPT (12-48-fold) and alkaline phosphatase (5-6-fold) activities in high dose males and females, both after 1 and 3 months of exposure.

Histological evaluation found the following effects in the liver: hepatocellular vacuolation was found in 4 top dose females (grade 3). In males this was grade 1 (1 animal) and grade 3 (1 animal) at the mid dose and grade 1 (1 animal), grade 3 (1 animal) and grade 4 (1 animal) at the top dose. Single cell necrosis was found in 3 top dose males and 3 top dose females (both grade 1). Periportal fibrosis was found in 1 top dose male and 2 top dose females, both grade 3. Kupffer cell proliferation was found in 2 mid dose females (grade 1) and 3 top dose males (grade 2).

Pathology identified two females and one male in the top dose group with tan discoloration and mottling in liver. Evidence of chronic stomach inflammation was seen in 2/4 males and 3/4 females at the top dose.

In a non-guideline combined 1 year/6 month supporting study, Beagle dogs were administered AMP-HCl via the dietary route. In the one-year group, 4 dogs/sex/dose were used, in the 6-month group, 2 dogs/sex/dose were used. Dietary concentrations were 0, 1.1, 11 or 110 ppm.

No signs of systemic toxicity were noted through the duration of the study.

No effects on male organ weights were noted. In females, after 12 months decreased absolute liver weights were seen in the low dose and top dose groups (-23.1% and -15.4% respectively). Statistically significant decreases in thyroid weight were also found in the low and top dose groups (-20.6% and -15.4%)

Albumin (via serum electrophoresis) was slightly increased in high dose males after 9 (+6.6%) and 12 months (+7.6%) of administration but not in females (all $p<0.05$).

Rabbit studies

A dose-range finding study for OECD TG 414 was available. Groups of 3 female NZW rabbits/group were administered AMP-95 (adjusted for pH using NaOH or HCl. Final pH range 6.90-7.50) at doses of 10, 25, or 75 mg/kg bw/d by oral gavage.

There was one mortality at the top dose. Decreased body weight and food consumption were also noted, but no information regarding magnitude or incidence was available.

No effects were recorded at the mid or low dose.

In a prenatal developmental toxicity study, performed in accordance with OECD TG 414, groups of 20 female NZW rabbits/group were administered AMP-95 by oral gavage. Dose groups were 10, 25 or 75 mg/kg, which was adjusted for pH using sodium hydroxide or hydrochloric acid to give a final pH or between 6.64 and 7.47. The study spanned GD 7-28 and was GLP-compliant.

With regards to mortality at the top dose, 2/20 animals were found dead on GD 22, 17/20 were euthanised as moribund between GD 22-28. These deaths were attributed to liver toxicity. Two animals died in the control group, one due to gavage error (was replaced on GD 7 by a suitable extra rabbit) and the second could not be determined.

In the liver, hepatocellular vacuolation was seen in all dose groups: 1/20 (minimal); 9/20 (minimal to mild) and 10/11 (minimal to moderate) in the low, mid and top doses respectively. Ductular hyperplasia was seen in the mid and top dose groups 4/20 (minimal) and 9/11 (minimal) respectively.

In the top dose group, vacuolar degeneration/necrosis was noted in all examined animals, characterised as minimal to moderate. Multifocal necrosis was also seen in 4/11 animals (mild to moderate).

Monkey studies

A 5-day non-guideline study was conducted in Resus monkeys: 1/sex/dose group were administered 0, 500, or 1000 mg/kg bw/d of AMP regular (industrial grade) at pH >11 by oral gavage. Administration was for 5 days total followed by a 10-day recovery period.

Both animals died at the top dose.

At both doses the monkeys lost body weight (cited by RAC as both about -11%). Haematology in the low dose monkey after the 10-day recovery showed a 7% decrease in haematocrit and 11% increase in WBC counts compared to the values before dosing. Clinical biochemistry showed marked electrolyte disturbance (29% decrease in K+, 69% decrease in Ca2+) and indications of liver damage (26% increased BUN, 79% increased SGPT, 33% increased CPK, 189% increased OCT). Gross pathology showed no effects after recovery period and histopathology of the liver was normal.

Inhalation route

A 5-day non-guideline inhalation study was available. Groups of 5 SD rats/sex were administered 0, 700, 1400 or 2000 mg/m^3 of AMP regular, aerosolised via nebuliser for 6 hours/day by the nose only route.

There were no mortalities through the duration of the treatment period and clinical observations (after exposure) were redness around the eyes and/or nose fur and wet inguinal fur for all animals in all groups.

Animals in the mid and top dose groups showed a statistically significant decrease in body weight; -14% in males and -9.6% in females; and -9.1% in females only, respectively. A statistically significant increase in adrenal weights in top dose males was noted (+ 28.6%). Relative kidney weights were statistically significantly increased in the mid and top dose females; +19.5% and +15% respectively.

Relative liver weights were statistically significantly increased in the mid and top dose groups; +19.6% in males and +20.9% in females; +20.5% in males and +25% in females. Changes in liver weights were accompanied by liver vacuolation in both sexes in the mid and top dose groups. These were characterised as 3/5 males (minimal) and 4/5 females (minimal) 1/5 females (mild) at the mid dose and 5/5 males (minimal) and 4/4 females (minimal) at the top dose.

Skin necrosis was noted in mid and top dose animals: characterised as mild to moderate in males and moderate to marked in females in the mid dose and mild to marked in males and moderate to marked in females in the top dose. Skin ulceration and hyperplasia were also noted in both groups.

Dermal route

In a non-guideline dermal developmental toxicity probe groups of 8 female CD(SD) rats/group were administered 0, 100, 300 and 400 mg/kg bw/d AMP-HCl from GD 6-20 dermally for 6 hours per day (occlusive non-absorbent cotton applied to a clipped area on the back). This was equivalent to 71, 213 and 284 mg AMP/kg bw/d. The pH was adjusted to 9.5 ± 0.15 using sodium hydroxide. There were no adverse findings in the study.

Comparison with the classification criteria

The results of animal studies described above are summarised and compared with their relevant guidance values in the table below:

Table 8: Summary of repeated dose toxicity study results and their comparison with the guidance values, adapted from Table 3 of the RAC opinion.

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
5-day non-guideline Long-Evans rats	2500 mg/kg bw/d Mortalities: 5/5 m, 5/5 f top dose	Cat. 1 AMP: ≤ 180	STOT RE 2 (mortality)

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
0, 500, 1000 or 2500 mg/kg bw/d AMP regular (industrial grade) pH >11 oral gavage	1000 mg/kg bw/d Mortalities: 2/5 f ↓ bw males	180 < Cat. 2 AMP ≤ 1800	
A 14-day range finding (Crl:CD(SD)IG SBR) rats 0, 100, 300, 600 or 800 mg/kg bw/d AMP-HCl diet.	800 mg/kg bw/d Liver weights: abs. ↑ 12.3%, rel. ↑ 12.2%	Cat. 1 AMP: ≤ 64 64 < Cat. 2 AMP ≤ 643	no classification
OECD TG 414. rats 0, 30, 100, or 300 mg/kg AMP-95 (adjusted for pH 6.72-7.46 oral gavage GD 6-20.	300 mg/kg bw/d ↑ 14.3% liver weight Hepatocellular vacuolation 23/25 Focal necrosis 2/25 multifocal necrosis 1/25. 100 mg/kg bw/d Hepatocellular vacuolation 19/25 Focal necrosis 3/25	Cat. 1 AMP: ≤ 64 64 < Cat. 2 AMP ≤ 643	STOT RE 2 (liver)
EOGRTS cohorts 1A and 1B without extension CD(SD) rats	200 mg/kg bw/d Liver weights ↑ 11.6% hepatocellular vacuolation 24/30 m	Cat. 1: AMP-HCl: ≤ 7.7 Cat. 2: AMP-HCl ≤ 77	No classification

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
0, 50, 100 or 200 mg/kg bw/d AMP-HCl. Doses equivalent to 0, 35, 71 and 142 mg/kg bw/d AMP dietary route	Kidney weight ↑ 7.9% 100 mg/kg bw/d Kidney weight ↑ 11.6% 50 mg/kg bw/d 1 euthanised	Cat. 1: AMP: ≤ 5.5 Cat. 2: AMP ≤ 55	
RDT OECD 421 CD rats 0, 100, 300 and 1000 mg/kg bw/d AMP-HCl dietary route. equivalent to 0, 71, 213 and 710 mg AMP/kg bw/d	1000 mg/kg bw/d Liver weights abs. ↑ 16.6% rel. ↑ 11.2% m only Kidney weights abs. ↑ 21.3% rel. ↑ 15.8%.	Cat. 1 AMP: ≤ 64 64 < Cat. 2 AMP ≤ 643	No classification
8 week non guideline CD rats AMP 78/89, 162/174, 314/345, 625/717 and 1359/1355 mg/kg bw/d. Dietary route	1359/1355 mg/kg bw/d. Mortality 2/10 f; ↓ bw gain (m -16.3%, f -21.8%) alopecia (3m and 6f), focal skin ulceration (3m and 5f) hepatocellular vacuolation (slight to moderate) (m 10/10, f 8/10) 625/717 mg/kg bw/d: hepatocellular vacuolation (very slight to moderate) (m 10/10, 7/10)	Cat. 1 AMP: ≤ 6.2 6.2 < Cat. 2 AMP ≤ 62	No classification

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
Non GLP Sprague Dawley rat 90-92d AMP-95/HCl 1.9/2.2, 11/13, 19/23 and 187/233 mg APM/kg bw (M/F) Dietary route Viral infection reported, not assumed to confound the study	187/233 mg APM/kg bw At 1 month: total bilirubine ↓ At 3 months: ↑SGOT (m, f), ↑LDH (m, f), ↑alkaline phosphatase (f) ↓total protein (f), and ↓globulin levels (f) Rel. kidney weights ↑ (m, +11.1%) ↑ absolute (+19.8%) and relative (+14.6%) spleen weights (f) patchy hepatocellular vacuolization (minimal to moderate) in the liver of 3/20 males and 4/20 females (only done in high dose group	Cat. 1: AMP ≤ 10 10 < Cat. 2 AMP ≤ 100	No classification
non-guideline 13 week CD rats. AMP regular 0, 500, 750, 1100 and 1700 mg/kg bw/d by oral gavage. (1) Without pH adjustment, pH 11+ (2) with pH adjustment (HCl), pH 7 (purple colour was	**pH 11** 1700 mg/kg bw/d Mortality: m 10/10, f 9/10 m 'marked' lower bw gain, f no effect Proteinuria 1100 mg/kg bw/d Mortality: m 3/10, f 8/10 m lower bw gain, f no effect ↓hematocrit (m, -9%), ↓hemoglobin (m, -9.7%), ↓red	Cat. 1: AMP ≤ 10 10 < Cat. 2 AMP ≤ 100	No classification

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
decolorised with activated charcoal,	blood cell count (m, -19.8%); ↓SGPT (m, -36%) Proteinuria 750 mg/kg bw/d Mortality: m 3/10, f 4/10 ↓Red blood cell count (m, -14.8%). Proteinuria 500 mg/kg bw/d: Mortality: m 2/10, f 0/10 ↓Red blood cell count (m, -16.3%) Proteinuria **pH 7** 1700 mg/kg bw/d: Hyperactivity and hyperirritability, loss of hair, skin ulceration ↓hematocrit (m, -13%) and ↓hemoglobin (m, -11.7%) ↑ SGPT values (f, +62%, m, +176%), ↑OCT (m, +156%), ↓total protein (m, -9.9%; f, -8%) Histopath. findings in some males (e.g. kidney: minimal hydronephrosis, interstitial lymphocytic infiltations; liver: minimal degree of fatty metamorphosis in liver, pyknotic nuclei, focal accumulation of macrophages and lymphocytes) 1100 mg/kg bw/d: ↑ SGPT values (m, +530%), ↑OCT (m, +273%)		

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
8 week non-guideline CD-1 mice AMP regular (P-1826) (no purity indicated, unclear identity, no info on pH adjustment) 0, 200, 400, 800, 1600 and 3200 ppm dietary	501/685 mg/kg bw/d (M/F) No effects	Cat. 1 AMP: ≤ 16 16 < Cat. 2 AMP ≤ 160	No classification
28 day range finder Beagle dog Uknown form AMP (described as P-1826, no purity indicated, unclear identity) 600, 1800, 5400 or 16200 ppm. Equivalent to 20/19, 54/70, 62/183 and 80/108 mg AMP/kg bw/d dietary route.	80/108 mg AMP/kg bw/d: Soft stools and/or diarrhoea, dry nose and mouth bw loss m (-29.5%) and f (-14.8%), ↓ feed consumption m (87.8%) and f (-80%) ↓ absolute and rel. liver weight in m (-41.4% / -6.6%) and absolute in f (-29.6% / +3.3%) Liver: hepatocellular vacuolation in m and f (moderate to marked), fibroplasia m (very slight centrilobular), liver cell necrosis m (scattered foci) ↑ AP and SGPT activity, ↑ SGOT activity 62/183 mg AMP/kg bw/d:	Cat. 1 AMP: ≤ 32 32 < Cat. 2 AMP ≤ 320	STOT RE 2 (liver)

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
	Soft stools and/or diarrhoea bw loss m (-13.7%), reduced feed consumption m (-68%) ↓ absolute and rel. liver weight m (-38.6% / -20%) and f (-15% / -13.3%) Liver: hepatocellular vacuolation in m and f (slight to moderate), fibroplasia f (slight centrilobular), liver cell necrosis m and f (small foci, centrilobular), bile duct proliferation f (slight) ↑ AP and SGPT activity, ↑ SGOT activity 54/70 mg AMP/kg bw/d Soft stools and/or diarrhoea Liver: hepatocellular vacuolation in m and f (very slight to slight), fibroplasia m (slight centrilobular) ↑ AP and SGPT activity		
Non-guideline (OECD TG 409) 3 months Beagle dogs AMP-95/HCl 0, 25, 600 and 2500 ppm, equivalent to 0.78/0.85, 17/17 and 81/81 mg	81/81 mg AMP/kg bw/d: body weight ↓(not signif., ~10%) ↑ SGOT (2-4 fold), ↑SGPT (12-48-fold) and ↑ Alkaline Phosphatase (5-6-fold) Liver: vacuolation 3/4 m and 4/4 f (lipid deposition), periportal cirrhosis, bile duct hyperplasia in 2/4 m, single cell necrosis in 3/4 m, 3/4 f, periportal fibrosis in 1/4 m	Cat. 1 AMP: ≤ 10 10 < Cat. 2 AMP ≤ 100	STOT RE 2 (liver)

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
AMP/kg bw/d (M/F).	and 2/4 f Stomach chronic inflamm 2/4 m, 3/4 f 17/17 mg AMP/kg bw/d: hepatocellular vacuolization 2/4 m		
Non-guideline 1 year/6 month Beagle dogs AMP-HCl 0, 1.1, 11 or 110 ppm. Dietary route	2.7/2.4 mg AMP/kg bw/d liver weights ↓ in females in the low (-23.1%) and the high dose (-15.4%) thyroid weight ↓ in the low (-20.6%) and high dose (-26.7%) (all p	Cat. 1 AMP: ≤ 2.5 2.5 < Cat. 2 AMP ≤ 25	No classification
Range finding for OECD TG 414 Female NZW rabbits AMP-95 (adjusted for pH using NaOH or HCl. Final pH range 6.90-7.50) 10, 25, or 75 mg/kg bw/d Oral gavage.	75 mg/kg bw/d: Mortality 1/3 Body weight ↓, food consumption ↓	Cat. 1 AMP: ≤ 30 30 < Cat. 2 AMP ≤ 300	No classification
OECD TG 414,	75 mg/kg bw Mortality: 2/20 found dead (GD 22), 17/20 euthanized as moribund	Cat. 1 AMP: ≤ 41	STOT RE 2 (liver)

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
Female NZW rabbits AMP-95 (adjusted for pH using NaOH or HCl final pH or between 6.64 and 7.47) 10, 25 or 75 mg/kg, GD 7-28 Oral gavage	(GD 22 – 28) (attributed to liver toxicity) Liver: vacuolar degeneration/necrosis 11/11 (minimal to moderate), multifocal necrosis 4/11 (mild to moderate), ductular hyperplasia 9/11 (minimal), hepatocellular vacuolation 10/11 (minimal to moderate) 25 mg/kg bw/d: Liver, ductular hyperplasia 4/20 (minimal), hepatocellular vacuolation 9/20 (minimal to mild) 10 mg/kg bw/d: Liver, hepatocellular vacuolation 1/20 (minimal)	41 < Cat. 2 AMP ≤ 410	
5 day non-guideline Resus monkeys: 0, 500, or 1000 mg/kg bw/d AMP regular (industrial grade) pH >11 Oral gavage. 10 day recovery period	1000 mg/kg bw/d: Mortality 2/2 (1m+1f), bw loss 500 mg/kg bw/d: bw loss ↓ haematocrit (-7%), ↑ WBC counts (+11%) ↓ K+ (-26%), ↓ Ca2+ (-69%), ↑ BUN (+26%) , ↑SGPT (+79%), ↑CPK (+33%), 189% increased ↑OCT (189%)	Cat. 1 AMP: ≤ 180 180 < Cat. 2 AMP ≤ 1800	STOT RE 2 (mortality)

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
5 day non-guideline SD rats 0, 700, 1400 or 2000 mg/m^3 AMP regular, aerosolised via nebuliser (nose only) 6 hours/day	2000 mg/m³: ↓Terminal bw f -9.1% ↑Rel. adrenal weight m +28.6%, ↑Rel. liver weight m +20.5%, f + 25.0%, ↑Rel. kidney weight f +15.0% Liver vacuolation m, f (minimal to mild) Skin necrosis m (mild to marked, f (moderate to marked), skin ulceration, hyperplasia 1400 mg/m³: ↓Terminal bw m -14.0%, f -9.6% ↑Rel. liver weight m +19.6%, f + 20.9%, ↑Rel. kidney weight f +19.5% Liver vacuolation m, f Skin necrosis m (mild to moderate, f (moderate to marked), skin ulceration, hyperplasia	Cat. 1: AMP: ≤ 360 mg/m3/6h/d 360 < Cat. 2 AMP ≤ 3600 mg/m3/6h/d	STOT RE 2 (liver)
non-guideline dermal developmental toxicity probe female CD(SD) rats	No effects on bw, organ weights (liver, kidney) Skin: scaling and scabbing (progressing over time) at 300 mg/kg bw/d	Cat. 1 AMP: C ≤ 120 120 < Cat. 2 AMP ≤ 600	No classification

Study description	Observations	(Extrapolated) guidance value in mg/kg bw/d	Supported classification
0, 100, 300 and 400 mg/kg bw/d AMP-HCl GD 6-20 6 hours/day (occlusive dressing). Equivalent to 71, 213 and 284 mg AMP/kg bw/d. pH adjusted to 9.5 ± 0.15 using sodium hydroxide			

According to the Guidance on the Application of the CLP Criteria (ECHA, 2024b), Section 3.9.2.3.2: 'If there are differences in effects at the GV between studies with different duration then more weight is usually given to studies of a longer duration (28 days or more)'. This consideration was taken into account by RAC in their assessment.

RAC's summary of the effects of AMP-HCl and AMP in the repeated dose toxicity studies is as follows:

Text from pages 30-31 of the RAC opinion (ECHA, 2026):

Noting that AMP-HCl in the repeated-dose toxicity studies at doses within relevant guidance values for STOT RE 2 has induced hepatocellular vacuolation with lipid deposition, periportal cirrhosis and periportal fibrosis with increased activity of SGOT (2-4-fold), SGPT (12-48-fold) and alkaline phosphatase (5-6-fold) in dogs (1981a), hepatocellular vacuolation in rats (Anonymous, 2021), mortality attributed to liver toxicity, vacuolar degeneration/necrosis of liver, multifocal necrosis, hepatocellular vacuolation in rabbits (Anonymous, 2020a) RAC is of the opinion that classification STOT RE 2; H373 (liver) for this substance is warranted. Taking into account that AMP in repeated-dose toxicity studies at doses within relevant guidance values for STOT RE 2 has induced hepatocellular vacuolation, focal and multifocal necrosis in pregnant female rats

(Anonymous, 2020b), hepatocellular vacuolation, fibroplasia and liver cell necrosis with increased activity of AP, SGPT and SGOT activity in Beagle dogs (Anonymous, 1976c), vacuolar degeneration/necrosis of liver, liver multifocal necrosis, hepatocellular vacuolation in pregnant rabbits (Anonymous, 2020a), mortality in monkeys (Anonymous 1977b), significant increase of relative liver weight with vacuolation of hepatocytes in rats exposed to AMP by inhalation (Anonymous (2017) RAC considers that classification STOT RE 2; H373 (liver) for this substance is warranted.

RAC notes that alopecia noted in 3 out of 10 males and in 6 out of 10 females as well as focal skin ulceration in 3 males and in 5 females in the 8 week dietary study in rats (Anonymous, 1976b) exposed to AMP was not induced by systemic toxicity, but was rather due to prolonged local skin exposure to AMP present in the diet. Not neutralised AMP is known for its skin irritation/properties due to its high pH. No skin ulceration or irritation were noted in other repeated-dose toxicity or reproduction toxicity studies in which rats were exposed via diet to AMP-HCl at doses up to 1000 mg/kg bw/d) (Anonymous, 2021; Anonymous, 1981a/b; P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | echa.europa.eu 31 Anonymous, 2005a). Also the effects in nasal cavity (atrophy goblet cells and olfactory epithelium; infiltration, metaplasia, ulceration) as well as skin necrosis skin ulceration observed in male and female rats exposed 6h/d for 5 days (nose-only) to 10% aqueous solution of AMP by inhalation at concentration of 700, 1400 and 2000 mg/m3 (Anonymous, 2017) were considered induced by local skin irritation/corrosion properties of AMP, rather than systemic toxicity. These effects are covered by classification of AMP as Skin Corr. 1, H314.

End of RAC text

Overall, RAC concluded that AMP warranted classification as **STOT RE 2; H373 (May cause damage to liver through prolonged or repeated exposure)**.

Classification proposed by the Agency:

The Agency agrees with RAC's conclusion on classification. AMP warrants classification as **STOT RE 2; H373 (May cause damage to liver through prolonged or repeated exposure)**.

Germ cell mutagenicity

Not assessed in the CLH report or RAC opinion.

Carcinogenicity

Not assessed in the CLH report or RAC opinion.

Reproductive toxicity

Classification agreed by RAC:

Adverse effects on sexual function and fertility

There were two studies available for the consideration of potential effects on sexual function and fertility of AMP, both conducted with AMP-HCl. The first was an Extended One Generation Reproductive Toxicity study (EOGRTS) – cohorts 1A and 1B without extension, which was GLP-compliant. In the F0 generation, groups of 25 CD(SD) rats/sex/dose were administered AMP-HCl at dose levels of 0, 50 and 100 mg/kg bw/d, and 30/sex administered a top dose of 200 mg/kg bw/d. Doses were calculated to be equivalent to 0, 35, 71 and 142 mg/kg bw/d AMP (using a 0.71 conversion rate) and were administered via the dietary route. The F0 generation were dosed for at least 70 consecutive days before mating and until scheduled necropsy (females were dosed throughout mating, gestation and lactation).

In the F0 generation, one female at the low dose group was euthanised in extremis on lactation day (LD 8), due to hunched posture, thin/pale body, red material around the nose, pale/cool extremities, uterine adhesion, 1 mummified foetus, 2 autolysed foetuses in utero and evidence of a uterine infection. Signs of systemic toxicity in treatment groups were sporadic, with either no dose-response relationship or occurring at similar incidences to control animals; these included hunched posture, hair loss and scabbing.

Increased liver weights were noted in top dose males only (absolute +11.6%; relative 12.7%). The increase was statistically significant and accompanied by moderate hepatocellular vacuolation in 24/30 males. Kidney weight was statistically significantly increased in mid and top dose males (absolute +7.9% and +9.1% and relative +11% and +10.1% at 100 and 200 mg/kg bw/d, respectively).

Non-pregnant females were observed in the control, low and mid dose groups, at incidences of 3/25, 2/25 and 3/25, respectively. All mated pairs in the top dose group resulted in pregnant females, so this effect was not considered to be treatment-related. The mean gestation lengths in the 0, 50, 100, and 200 mg/kg bw/d groups were 21.8, 22.2, 21.8, and 22.1 days, respectively, with statistically significant increases compared to the control at 50 and 200 mg/kg bw/d. However, these values were within or close to the HCD (mean of 21.8 and range of 20.9-22.1) and did not show a dose-response relationship. No effects of AMP-HCl on sperm parameters (mean testicular and epididymal sperm numbers

and sperm production rate, motility, progressive motility, and morphology) were seen in any dose group.

Thyroid hormones were also not affected. There were also no significant effects on haematology, coagulation, clinical chemistry or urinalysis parameters. Gross-pathology showed no test-substance related findings. Numbers of implantation sites were unaffected by treatment. A statistically significant higher number of unaccounted-for sites (calculated as number of former implantation sites – number of pups born) compared to the control group was noted in the 200 mg/kg/d group. This difference was attributed to one single female with 13 unaccounted-for sites.

In the F1 generation, there were no noteworthy clinical signs of toxicity or effects on body weight, body weight gain or food consumption. A statistically significantly higher mean oestrous cycle length was noted at the top dose: 3.8 ± 0.45, 4.1 ± 0.94, 4.2 ± 0.89 and 4.8 ± 1.66 days at 0, 50, 100, and 200 mg/kg bw/d respectively. However, RAC noted that the increase was within the HCD range, whilst the concurrent control value was below the HCD (3.9 – 5.2 days).

HCD were obtained from a range of studies conducted between June 2006 and May 2018. RAC acknowledged that as the EOGRTS was conducted in 2021, the HCD were not contemporary to the study, noting that the Guidance on the Application of the CLP Criteria (ECHA, 2024b) recommends that HCD should be obtained from studies conducted within a period of up to 5 years around the study being evaluated. However, the HCD were conducted in the same test strain and laboratory. Therefore, RAC concluded that the HCD were of limited reliability, but still relevant for evaluation of the EOGRTS.

The second study available to assess adverse effects on sexual function and fertility was a reproduction/developmental toxicity screening study, conducted in line with OECD TG 421 and GLP. Groups of 12 CD rats/sex/group were administered AMP-HCl via the dietary route. Doses of AMP-HCL were 0, 100, 300 and 1000 mg/kg bw/d, which was equivalent to 0, 71, 213 and 710 mg AMP/kg bw/d. Females were dosed for 2 weeks prior to breeding, through breeding, gestation and until PND 4 (total of 42-49 days) and males were dosed 2 weeks prior to breeding, through breeding until necropsy (total of 38 days). Pups were euthanised on PND 4.

At the top dose there were statistically significant increases in absolute and relative liver and kidney weights in males. In the liver, absolute weights increased by 16.6% and relative weights increased by 11.2%. In the kidney, absolute weights increased by 21.3% and relative weights by 15.8%. Females did not show the same effect. There were no treatment-related effects on mortality or body weight.

In addition to the animal data, the DS also provided several US clinical studies on the pharmaceutical Pamabrom, which is used as a diuretic agent for relief of symptoms during menstruation. Pamabrom is an AMP salt of 8-bromotheophylline (equimolar mixture of

74.4% w/w 8-bromotheophylline (CAS No. 10381-75-6) and 25.6% w/w AMP). A bioequivalence study (Anonymous, 2019a) concluded that AMP from Pamabrom and AMP behave similarly. Overall, the DS considered that the studies were not appropriate to make a sound conclusion on the adverse effects of Pamabrom in humans. RAC noted that none of the studies investigated early implantation loss or other reproductive endpoints (except foetal movement). Therefore, these studies were not considered further by RAC.

Comparison with classification criteria

No effect of AMP-HCl on sexual function and fertility was noted in the F0 generation in the EOGRTS in rats at doses of 50, 100 or 200 mg AMP-HCl/kg bw/d (corresponding to 35, 71, 142 mg AMP/kg bw/d). No general toxicity was observed in treated females; dose-related organ weight changes were seen in the livers and kidneys of males. The increased liver weights occurred alongside hepatocellular vacuolation.

No effects on sexual function and fertility were observed in the reproduction/developmental screening study, at doses of 100, 300 or 1000 mg AMP HCl/kg bw/d.

As discussed in the 'Background' section of this technical report, RAC concluded that read-across from studies using AMP-HCl was appropriate for the reproductive toxicity assessment of AMP. In the absence of effects on sexual function and fertility in either study with AMP-HCl, RAC concluded that classification for this hazard was not warranted for AMP.

<u>Adverse effects on development</u>

For evaluation of adverse effects on development, RAC considered the EOGRTS and reproduction/developmental toxicity screening test, both conducted with AMP-HCl in rats and described in the previous section. In addition, three OECD TG 414 studies (rat and rabbit) and one developmental toxicity probe study (non-guideline, rat) were conducted with AMP (of different purity) adjusted to a pH between 6.6 and 9.5. The DS also presented a range of studies to investigate a possible mode of action (MOA) are available.

As described above, the EOGRTS was conducted according to OECD TG 453. Groups of 25 CD(SD) rats/sex/dose were administered dietary doses of AMP-HCl at 0, 50 and 100 mg/kg bw/d with a top dose group of 30 CD(SD) rats/sex being administered a dose of 200 mg/kg bw/d. Doses were equivalent to 0, 35, 71 and 142 mg/kg bw/d AMP.

As described above, increased liver weights were noted in top dose males only (absolute +11.6%; relative 12.7%). The increase was statistically significant and accompanied by moderate hepatocellular vacuolation in 24/30 males. Kidney weight was statistically significantly increased in mid and top dose males (absolute +7.9% and +9.1% and relative +11% and +10.1% at 100 and 200 mg/kg bw/d, respectively).

There were no effects on the numbers of implantation sites in females in the F0 treatment groups. However, RAC noted that the numbers of post-implantation losses in the F0 generation increased at the top dose compared to the control (incidences of 6.9%, 11.5%, 8.9% and 28.9% in the 0, 50, 100 and 200 mg/kg bw/d groups, respectively). Post-implantation loss at the top dose was largely attributed to 4 females with total resorptions, which RAC considered to be indicative of possible developmental toxicity. In the top dose group, mean live litter sizes were slightly smaller, but this was not statistically significant: 12.8 ± 3.64, 11.9 ± 4.37, 13.4 ± 2.95 and 11.3 ± 4.15 for 0, 50, 100, and 200 mg/kg bw/d respectively.

The reproduction/developmental toxicity screening test (also discussed above) was conducted in line with OECD TG 421 and GLP. Groups of 12 CD rats/sex/group were administered AMP-HCl via the dietary route. Doses of AMP-HCL were 0, 100, 300 and 1000 mg/kg bw/d, which was equivalent to 0, 71, 213 and 710 mg AMP/kg bw/d. Females were dosed 2 weeks prior to breeding, through breeding, gestation and until PND 4 (total of 42-49 days) and males were dosed 2 weeks prior to breeding, through breeding until necropsy (total of 38 days). Pups were euthanised on PND 4.

Post implantation losses were noted at the mid and top doses. At the top dose, there was 100% post implantation loss. In the mid dose, 70% post implantation loss was noted, along with associated effects: decreased litter size (mean of 7.4 compared with 14.1 in concurrent controls), increased pup body weight in males (mean of 8.2 g compared with 7.1g in concurrent controls), decreased body weight on gestation day (GD) 20 (-5.5%, not statistically significant) and a statistically significant 40% reduction in body weight gain between GD 14 and GD 20.

Histopathology showed an increased number of pigment-laden macrophages beneath the uterine mucosa in mid and high dose females with total resorptions.

In a non-guideline dermal developmental toxicity probe study, groups of 8 female CD(SD) rats/group were administered 0, 100, 300 and 400 mg/kg bw/d AMP-HCl from GD 6-20 dermally for 6 hours per day, using occlusive non-absorbent cotton applied to a clipped area on the back. Dose levels were equivalent to 71, 213 and 284 mg AMP/kg bw/d. pH was adjusted to 9.5 ± 0.15 using sodium hydroxide.

No dermal observations were reported during the course of the study at any dose level, only a dose-dependant increase in slight scaling was seen in exposed animals. There were no effects on body weight or body weight gain, no effects on liver or kidney weights and no pathological treatment related effects were found. No adverse effects on reproductive parameters were found at any dose.

A dermal prenatal developmental toxicity (PNDT) study was available, conducted in line with OECD TG 414. Groups of 26 female CD(SD) rats were administered ‘high purity grade’ AMP at doses of 30, 100 and 300 mg/kg/d which was adjusted to approximately pH

9.5 using hydrochloric acid. AMP was administered dermally for 6 hours per day over GD 6-20. No adverse effects on reproductive parameters were found at any dose.

In a non-guideline dose range finding study, groups of 3 female NZW rabbits/group were administered AMP-95 at doses of 10, 25 and 75 mg/kg by oral gavage. Doses were adjusted for pH using sodium hydroxide or hydrochloric acid to have a final pH of 6.9-7.5. The study duration was 22 days. No adverse effects on reproductive parameters were found at any dose.

In a prenatal developmental toxicity study, performed in accordance with OECD TG 414, groups of 20 female NZW rabbits/group were administered AMP-95 by oral gavage. Dose groups were 10, 25 or 75 mg/kg, which was adjusted for pH using sodium hydroxide or hydrochloric acid to give a final pH or between 6.64 and 7.47. The study spanned GD 7-28 and was GLP compliant. Severe maternal toxicity occurred at the top dose: 2/20 were found dead on GD 22, 17/20 were euthanised between GD 22 and 28. There were multiple findings in the liver, which are detailed in the STOT RE section.

At the top dose, total litter loss was seen in 6 rabbits; 12 rabbits had live foetuses on the day of unscheduled death.

Persistent Truncus Arteriosus (PTA) was seen in 3 foetuses in 2 different litters at the mid dose and 2 foetuses in 2 different litters at the low dose. At the top dose, foetuses could not be evaluated for this due to the rate of maternal mortality. PTA was not found in the concurrent control and the incidence was outside of the HCD (mean of 0.22% for foetuses and 2.2% for litters). RAC considered that PTA seen in a total five foetuses (1.05% and 1.49% in the low and mid dose groups, respectively) to be a rare but test substance-related and biologically significant malformation.

Discussion of MOA

RAC included the following discussion of a possible MOA, based on the MOA studies presented in the CLH report:

Text taken from pages 25-28 of the RAC opinion (ECHA, 2026)

Additional considerations on possible mode of action

Changes in choline absorption and physiological function may be responsible for post implantation loss of embryos induced by administration of AMP. Choline is the essential nutrient and constituent of cell and mitochondrial membranes and of the neurotransmitter acetylcholine and it influences the lipid metabolism. The major fates for choline are (1) to be phosphorylated and used to make phospholipids, or (2) to be oxidized and used as a donor of methyl-groups. Of special importance in this context is phosphatidylcholine, which is necessary for the packaging and export of triglycerides in very low density lipoprotein

(VLDL) (Corbin und Zeisel (2012). In the study of mechanism of action of the effect of AMP-HCl on metabolism of choline (Anonymous, 2006c) AMP-HCl was given to female rats via diet at 0 or 300 mg/kg bw/d for approximately two weeks prior to breeding, continuing throughout breeding (up to two weeks), until GD 13. All females of the 300 mg/kg bw/d group had partial litter loss to varying degrees. The increase in post-implantation loss (67.0%) was reflected by a decrease in mean number of viable foetuses per litter (-57%) and an increased mean number of resorptions per litter (10-fold increase), when compared to control. In three out of six exposed females, multifocal hepatocellular vacuolisation, consistent with fatty change, visible as readily conspicuous, larger and more numerous lipid droplets than in the controls mainly in periportal/ midzonal regions the was found. The levels of phosphocholine, a primary storage form of choline in vivo, was decreased (-21.6%) in treated females, while levels of glycerophosphocholine, generally reflecting de novo choline synthesis via breakdown of phosphatidyl choline, were elevated (+267,5%). The minimal elevation in betaine and the 26% elevation in choline levels of treated rats in the present study is consistent with an elevated level of choline formation from degradation of phosphatidyl choline and subsequent oxidation to maintain methylation status of the liver. Combined with the known choline depression caused by pregnancy in general, the data indicate that lipid accumulation and elevated resorptions after treatment with AMP-HCl may be the consequence of phosphocholine deficiency. In an in vitro study (Anonymous, 2006a) AMP-HCl caused dose-dependent decrease in the uptake of 3H-choline by Chinese hamster ovary (CHO) cells in the absence of severe toxicity (no significant differences in protein content between treated and control cultures) with an approximate EC50 of 8.71-14.79 mM. In an in vitro whole embryo culture study (Anonymous, 2008) AMP-HCl at concentration of ~8 µg/mL, AMP corresponding to the serum concentration of AMP on GD14 in pregnant rats exposed to 300 mg AMP-HCl/kg bw/d in diet (see Anonymous, 2009c) did not affect viability, visceral yolk sac circulation and growth of embryos. Therefore, the authors of the study concluded that direct exposure of embryos to AMP-HCl is not sufficient to cause embryotoxicity and thereby suggesting an indirect or maternally mediated mode of action for the post-implantation loss which was seen in seen several studies. In a study investigating the incidence of post-implantation loss (Anonymous, 2009a) it was shown that at GD14 the highest incidence of post-implantation loss was found when exposure to AMP HCl via diet or gavage at a dose level of 300 mg/kg bw/d started two weeks prior to breeding, through breeding (up to two weeks), and through GD1-8. In the diet exposure group, the incidence of post-implantation loss was 68.5%, while in the gavage exposure group it was 44.4%. When female rats were exposed by gavage at the same dose of AMP-HCl only during GD1-8 the post-implantation loss was 14.2%, which was still above the laboratory historical control range for both dietary and gavage exposure studies of similar duration (3.67%-9.69%). When exposure lasted during GD6-8 or GD9-11 post-implantation loss was within the HCD. The much higher incidence of post-implantation loss when exposure started prior to fertilisation (to GD 8) in relation to exposure during beginning of gestation only (GD1-8, GD6-8, or GD8-10) suggests a maternally mediated MoA, possibly associated with depletion of a factor

necessary to support post-implantation embryo development. In the study investigating the timing of embryolethality (Anonymous, 2009c), it was demonstrated that post-implantation loss due to oral exposure to AMP (300 mg/kg bw/d AMP HCl) occurs in rats already at a time before GD 8. Application of choline deficient diet alone (507 ppm choline) for two weeks prior to breeding, through breeding (up to two weeks) until GD14 did not increase the percentage of post implantation loss in comparison with a group of rats fed control diet (1800 ppm choline) (Anonymous, 2009c). Notably, application of choline-supplemented diet (9000 ppm choline) reduced percentage of post-implantation loss induced by exposure to 300 mg AMP-HCl/kg bw/d (39.2%) in comparison with post-implantation loss of 66.3% in animals exposed to the same dose of AMP-HCl but receiving control diet with standard concentration of choline (1800 ppm choline). The mean maternal blood concentrations of AMP on GD14 were similar between groups given the same dosage of AMP-HCl but receiving diet with control or supplemented level of choline (8.26 and 7.29 µg/g plasma, respectively), indicating that level of choline in the diet did not influence absorption and concentration of AMP in the blood of rats (Anonymous, 2009c). A 1.8-fold increase in choline and a 1.9-fold increase glycerophosphocholine relative to control group was found in rats given 300 mg AMP-HCl/kg bw/d and diet with control level of choline 1800 ppm choline), while in animals also receiving 300 mg/kg bw/d AMP-HCl, but with a diet supplemented with choline (9000 ppm choline) a partial normalisation of choline and a complete normalisation of glycerophosphocholine levels in maternal liver were shown. According to the study authors (Anonymous, 2009c) the results of the experiment indicated that post-implantation loss induced by AMP-HCl was not due to a simple choline deficiency; notably, the ability of choline to partially ameliorate the post-implantation effect suggests that some other aspect of phospholipid biochemistry could be involved in the MoA. In a study investigating the phospholipid profile of the liver and blood, gene expression of uterine tissue as well as embryotoxicity via whole embryo culture (Anonymous, 2010a) it was found that administration of 300 mg AMP-HCl/kg bw/d via diet for two weeks prior to breeding, through breeding (two weeks), and GD 1-6 may affect expression of genes in decidual swellings in samples of decidua taken from AMP treated rats. According to the study authors the gene expression data are consistent with the reproductive toxicity profile (post-implantation loss) of AMP-HCl as affected genes are coding proteins such as occludin, claudin 1, and claudin 2 which have been identified as integral tight junction membrane proteins that play a role in epithelial cell barrier maintenance and establishment of cell polarity. The published localisation of these down-regulated genes within the decidual swelling is consistent with histopathological findings of very slight or slight multifocal vacuolation within the uterine epithelium lining the conceptus in all of the seven treated animals. Oil red O staining did not reveal the presence of lipid within these vacuoles. Serial sections revealed increased amounts of karyorrhectic and pyknotic cellular debris in the uterine lumen of two treated females in the near vicinity of the embryos. Based on these results, the study authors concluded that, as a consequence of AMP-HCl exposure, normal implantation may be impaired through alterations in the tight junction signalling network. Ball et al. (2014) concluded that it is not possible to exclude

that the vacuoles in decidual swellings are a part of the resorption process rather than evidence of toxicity that causes the post-implantation loss. Considering data from in vivo studies: a) AMP-HCl exposure may impair normal implantation through alterations in down-regulation in genes of the tight junction signalling network in uterus (Anonymous, 2010a), and b) AMP-HCl treatment may affect cardiovascular development causing a rare heart malformation in rabbits (Anonymous 2020a), RAC considers plausible that the retinoid system could be a possible target of AMP MoA. Substantial experimental and epidemiological data have highlighted the retinoid system where retinoic acid (RA), a derivative of vitamin A, plays a key role during vertebrate development including the regulation of tight junctions associated proteins and the formation of the heart. Retinoids bind to RA and retinoid X receptors (RARs and RXRs) which then regulate tissue specific genes (https://doi.org/10.1016/j.mod.2016.12.002). The retinoid system is highly conserved throughout lower and higher animal taxa. Biological activity data for AMP in ToxCast (CompTox Dashboard accessed 7.5.2025) show positive results with retinoid RXR receptors binding in two tests.

End of RAC text

Comparison with classification criteria

RAC considered the following effects to be relevant for developmental toxicity classification:

- In a reproduction/developmental toxicity screening study, post implantation loss of 100% and 70% was reported after administration of AMP-HCl via diet at concentrations of 1000 or 300 mg/kg bw (corresponding to 710 or 213 mg AMP/kg bw/day), respectively (compared to a loss of 6.7% at 100 mg/kg bw/d and 9.7 in control).
- In a more recent EOGRTS, a dose of 200 mg AMP-HCl kg/bw/d), administered via the diet, led to post-implantation losses in high dose females (4 of 30 dams did not deliver).
- Post-implantation loss was also observed in mechanistic studies. In one based on OECD TG 422, where Crl:CD(SD) rats were exposed via diet to 0 or 300 mg/kg bw/d AMP-HCl, post implantation losses of 67.0% were documented (compared to 7.4% in the control). In a second study, Crl:CD(SD) rats were administered 300 mg AMP-HCl/kg bw/d; post-implantation losses of 68.5% were reported.
- In a PNDT in rabbits, a rare visceral malformation (PTA) was observed in 2/2 foetuses/litters at 10 mg/kg bw/d and 3/2 foetuses/litters at 25 mg/kg bw/d.

According to Table 3.5.1 (a) of the CLP Regulation, classification as a Category 1B reproductive toxicant is warranted where there is clear evidence of an adverse effect. Based on weight of evidence and read-across from studies on AMP-HCl, RAC concluded that AMP warranted classification as **Repr. 1B; H360D (May damage the unborn child)**.

Effects on or via lactation

The presence of AMP in breast milk was not specifically investigated in the available studies. However, RAC noted that there was no evidence of any adverse effects on or via lactation in either the EOGRTS or the reproduction/developmental screening study. Therefore, they concluded that classification for this hazard class was not warranted.

Classification proposed by the Agency:

The Agency agrees with RAC's conclusion on classification. **AMP warrants classification as Repr. 1B; H360D (May damage the unborn child)**. Classification is not warranted for adverse effects on sexual function and fertility or for effects on or via lactation.

Aspiration hazard

Not assessed in the CLH report or RAC opinion.

Environmental hazards

Hazardous to the aquatic environment

Classification agreed by RAC:

Rapid degradability of organic substances:

In their Opinion (ECHA, 2026), RAC agreed that AMP was **rapidly degradable** for the purpose of hazard classification based on the following data presented in the CLH report and background document (CLH, 2024):

- In a GLP, OECD TG 301F ready biodegradation study (Anon., 2009 in CLH, 2024) considered reliable with restrictions, 2-AMP (98.431%) was readily biodegradable, achieving 60.92% mean biodegradation after 28 days at a test concentration of 100 mg/L. Although the theoretical oxygen demand was initially calculated assuming nitrification ($ThOD_{NO_3}$), measured nitrite and nitrate concentrations at days 0 and 28 indicated that actual nitrification was negligible. Therefore, the dossier submitter (DS) recalculated biodegradation based on the theoretical oxygen demand without nitrification ($ThOD_{NH3}$). It was reported that the 10-day window began on day 20 (19.14% and 9.98% $ThOD_{NH_3}$ in the two replicates with an arithmetic mean of 14.6%), given the arithmetic mean degradation on day 19 was 5.6% $ThOD_{NH_3}$ (10.8% and 0.4% in the two replicates), indicating that the 10% threshold had not yet been reached. Based on $ThOD_{NH_3}$, the arithmetic mean

biodegradation was 60.92% (59.77% and 62.07% in the two replicates) at day 28 which is above the 60% threshold for mineralisation based on oxygen depletion. The positive control achieved greater than 60% degradation by day 10, confirming inoculum viability and that the test item was not toxic to the inoculum under test conditions. Overall, RAC considered that the 10-day window was met based on calculation of $ThOD_{NH_3}$.

- Supporting QSAR predictions (EPISuite, BIOWIN v4.10) indicated that AMP will be rapidly degradable in the environment and RAC agreed that AMP is within the model applicability domain.

Several additional ready biodegradability studies were available in the CLH report, of which five were considered by the DS to be unreliable or of unassignable reliability (CLH, 2024). It was noted that earlier studies were typically conducted using industrial-grade AMP, which contains the impurity 2-methylamino-2-methyl-1-propanol (MMAMP). As MMAMP is not readily biodegradable based on an OECD TG 301C study, the DS considered that its presence may have contributed to the lack of biodegradation observed in these older studies.

Overall, RAC agreed that AMP was **rapidly degradable** based on the substance being readily biodegradable and meeting the 10-day window in an OECD TG 301F study where more than 60% mineralisation of AMP was achieved within 28 days.

Bioaccumulation:

In their Opinion (ECHA, 2026), RAC agreed that AMP is **not bioaccumulative** for the purpose of hazard classification based on data in the CLH report (CLH, 2024).

The high water solubility of AMP (920 g/L) was noted, along with the likelihood that the substance is predominantly ionised at environmentally relevant pH, given the pKa of 9.81 reported in the CLH dossier (CLH, 2024). As a result, there is uncertainty associated with the derived log K_{OW} values. Experimentally derived log K_{OW} values were reported from two separate OECD TG 107 (shake flask method) studies for nnn: -0.63 (non-GLP, pH not measured) and -1.6 (GLP, pH 7.6 to 9.3).

Additionally, a QSAR estimated log K_{OW} of -0.74 for the neutral form of AMP (EPISuite, KOWWIN v1.68) and an estimated BCF value of 3.16 L/kg ww (EPISuite, BCFBAF v3.01) were provided.

A 3-day non-standard, non-GLP bioaccumulation test with the fish *Leuciscus idus* (Ide) was available using ^{14}C-AMP. The BCF was determined to be less than 1 L/kg, although the study was considered not reliable in the CLH report given exposure concentrations were not measured, and there was no information on steady-state or depuration (CLH, 2024).

Overall, despite the uncertainties introduced by the ionised state of the substance, RAC agreed that the available data does not indicate a potential for bioaccumulation, as all experimental and QSAR predicted log K_{OW} and BCF values are well below the hazard classification criterion of ≥4 and ≥500 L/kg respectively.

Aquatic toxicity:

Acute aquatic toxicity

In their Opinion (ECHA, 2026), RAC considered that relevant and reliable acute aquatic toxicity data were available for AMP for all three trophic levels and presented in the CLH report (CLH, 2024).

Three acute toxicity to fish tests employing three species were available, all resulting in endpoints above 1 mg/L. The most sensitive endpoint was a *Pleuronectes platessa* (European plaice) 96-hour LC_{50} of 184 mg/L (based on nominal concentrations, no analytical verification) from a non-GLP, EPA OPPTS 850.1075 study under semi-static conditions. The study was considered reliable with restrictions in the CLH report although various study deficiencies were noted; no test item purity, non-standard test species, no analytical verification of test concentrations and media pH of 10.3 (CLH, 2024).

Three aquatic invertebrate tests employing two species were available. The most sensitive endpoint was for *Crangon crangon* (shrimp) with a 96-hour LC_{50} of 179 mg/L (nominal, no analytical verification) from a non-GLP, EPA OPPTS 850.1045 study under semi-static conditions. The study was considered reliable with restrictions in the CLH report although various study deficiencies were noted; non-standard test species, no analytical verification of test concentrations and the guideline-recommended minimum of five test concentrations was not met (CLH, 2024).

A third invertebrate study with a more sensitive 24-hour EC_{50} endpoint of 65 mg/L was reported for *Daphnia magna* from a non-GLP OECD TG 202 study. However, limited study details were available with no information on control performance, test concentrations, or test conditions. Therefore, the DS considered the study reliability to be unassignable and concluded that the endpoint could not be used for hazard classification purposes.

Four studies, with three species were available on toxicity to algae. The most sensitive endpoints were for *Skeletonema costatum* and *Raphidocelis subcapitata* from two GLP, OECD TG 201 studies under static conditions, with both resulting in 96-hour E_rC_{50} values greater than 103 mg/L (based on mean measured concentrations). The study with *R. subcapitata* was considered reliable without restrictions by the DS, whereas the study with *S. costatum* was considered reliable with restrictions, as the mean coefficient of variation for section-by-section specific growth rates in control replicates was 36.1% (exceeding the OECD TG 201 criterion of 35%) .

RAC agreed that algae were the most sensitive taxonomic group, with the lowest short-term toxicity endpoint for AMP being the *R. subcapitata* and *S. costatum* 96-hour E_rC_{50} endpoints quoted as >103 mg/L. Given that this value and $L(E)C_{50}$ values for fish and invertebrates are all greater than the hazard classification criterion of 1 mg/L, RAC agreed that **no Aquatic Acute classification was required.**

Chronic aquatic toxicity

In their Opinion (ECHA, 2026), RAC noted that chronic aquatic toxicity data for AMP are not available for fish or invertebrates, with reliable chronic toxicity data only available for algae.

RAC noted that the *R. subcapitata* (study described above) resulted in a 72-hour E_rC_{10} of 68.8 mg/L, and a 72-hour NOE_rC of 6.6 mg/L, based on mean measured concentrations.

Supporting evidence from QSAR predicted values >1 mg/L (ECOSAR v.2.2 and ECOSAR v.1.11) for fish and aquatic invertebrates were also available in the CLH report (CLH, 2024).

RAC agreed that the lowest and most appropriate long-term toxicity endpoint was the 72-hour E_rC_{10} of 68.8 mg/L for *R. subcapitata*. Given this value is greater than the hazard classification criterion of 1 mg/L, and the substance is considered non-bioaccumulative and rapidly degradable, RAC agreed that **no Aquatic Chronic hazard classification was required.**

RAC Opinion:

RAC agreed to classify AMP as:

- **No Aquatic Acute hazard classification**
- **No Aquatic Chronic hazard classification**

Classification proposed by the Agency:

The Agency agrees that AMP is **rapidly degradable** based on a reliable OECD TG 301F ready biodegradability study where 60.92% (based on $ThOD_{NH_3}$) mean biodegradation of AMP was observed after 28 days. This level of degradation is above the 60% degradation threshold, and the 10-day window was met. This study is consistent with QSAR model predictions indicating AMP is rapidly biodegradable (EPISuite, BIOWIN v4.10).

An additional OECD TG 301F study is available (Anon., 2010 in CLH, 2024) indicating rapidly biodegradability, although this is considered only supporting evidence due to deviations from the standard methodology including given a test item concentration of 11.1 mg/L (guideline recommendation 100 mg/L) and the use of potentially pre-adapted activated sludge.

The Agency notes that two additional ready biodegradation studies (considered reliable with restriction) are available where AMP was considered not readily biodegradable. These tests employed AMP containing MMAMP. According to the CLH report (CLH, 2024), MMAMP is not readily biodegradable based on an OECD TG 301C study and the Agency agrees that the presence of MMAMP as an impurity may have influenced degradation. Given a positive result in a reliable ready biodegradability test is considered evidence of rapid degradability for hazard classification, the Agency agrees AMP is rapidly degradable.

The Agency agrees that AMP has **low potential for bioaccumulation** based on the available log K_{OW} values of -0.63 and -1.6 (experimental, OECD TG 107), and -0.74 (QSAR predicted, EPISuite, KOWWIN v1.68) which are consistent with the very high water solubility of the substance (920 g/L). The Agency also agrees that the experimental BCF of <1 L/kg is not reliable for hazard classification due to the non-standard test design and insufficient experimental details. The Agency notes that the log K_{OW} information is supported by a QSAR estimated BCF value of 3.16 L/kg ww (EPISuite, BCFBAF v3.01) although this value is subject to uncertainty given ionisation potential.

Overall, the Agency agrees that the available log K_{OW} values are below the hazard classification threshold of ≥4 and AMP is considered to have a low potential for bioaccumulation.

The Agency agrees that acute toxicity data are available for AMP across all three trophic levels. The Agency also agrees that all acute toxicity testing resulted in L(E)C_{50} values greater than 1 mg/L. The Agency notes that acute fish and invertebrate studies have uncertainties due to test design deviations and lack of analytical verification of test concentrations. The 24-hour EC_{50} of 65 mg/L for *D. magna* is the most sensitive acute endpoint. Whilst this is a non-standard duration endpoint and there is insufficient information to assess endpoint reliability for hazard classification, the endpoint is still above 1 mg/L and would not affect hazard classification.

The Agency also agrees that the 72-hour E_rC_{50} for *S. costatum* was above the highest treatment of 103 mg/L (based on mean measured concentrations).The Agency notes that while a concentration dependant growth rate response was observed in the algal growth inhibition study with *R. subcapitata*, less than 50% inhibition was observed at the highest treatment of 103 mg/L meaning the 72-hour E_rC_{50} is also considered above 103 mg/L (based on mean measured concentrations).

Given all acute toxicity endpoints are greater than 1 mg/L, the Agency agrees that **no Aquatic Acute hazard classification is required.**

The Agency agrees that relevant and reliable chronic toxicity data are only available for algae. The lowest reliable long term EC_x endpoint for AMP is the *R. subcapitata* 72-hour E_rC_{10} of 68.8 mg/L (based on mean measured concentrations). The *R. subcapitata* 72-

hour NOE_rC was 6.6 mg/L. The Agency also agrees that the 72-hour E_rC_{10} for *S. costatum* was above the highest treatment of 103 mg/L (based on mean measured concentrations) and the 72-hour NOErC was ≥103 mg/L.

Given AMP is rapidly degradable and non-bioaccumulative, a surrogate approach is not considered relevant.

As all available chronic toxicity values exceed 1 mg/L, the Agency agrees that **no Aquatic Chronic hazard classification is required.**

Other hazards

Hazardous to the ozone layer

Not assessed in the CLH report or RAC opinion.

Overall conclusion

The Agency has evaluated the RAC Opinion, its rationale and any additional scientific evidence that may have been made available to HSE against the criteria for classification and labelling in the GB CLP Regulation and technical guidance.

The Agency technical report **agrees** with the classification proposed by RAC for the following hazards:

Skin Corr. 1; H314 (Causes severe skin burns and eye damage), with SCLs:

Skin Corr. 1; H314: C ≥ 35%

Skin Irrit. 2; H315: 5% < C < 35%

Eye Dam. 1; H318 (Causes serious eye damage)

STOT RE 2; H373 (May cause damage to liver through prolonged or repeated exposure)

Repr. 1B; H360D (May damage the unborn child)

Not classified for adverse effects on sexual function and fertility, effects on or via lactation, aquatic acute or aquatic chronic hazards

Overall, the conclusion is to **agree** with the RAC opinion.

References

ECHA (2024a) Guidance on the Application of the CLP Criteria, Part 2: Physical Hazards. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 4.0, ref: ECHA-24-G-07-EN. Available at https://www.echa.europa.eu/

ECHA (2024b) Guidance on the Application of the CLP Criteria, Part 3: Health Hazards. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 5.0, ref: ECHA-24-G-06-EN. Available at https://www.echa.europa.eu/

ECHA (2024c) Guidance on the Application of the CLP Criteria, Part 4: Environmental Hazards; and Part 5: Additional Hazards. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 4.0, ref: ECHA-24-G-05-EN. Available at https://www.echa.europa.eu/

For all other references, please see the EU CLH report and the EU RAC opinion (available at: https://echa.europa.eu/registry-of-clh-intentions-until-outcome)

CLH (2024) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: 2-amino-2-methylpropanol; Date: 2024; Written by: Austria; Accessed date: 05/2026

ECHA (2026) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of 2-amino-2-methylpropanol; Reference CLH-O-0000007598-58-01/F; Date: 04/12/2025, Accessed date: 05/2026

Documents published as part of the EU CLH process: Source: European Chemicals Agency, http://echa.europa.eu/

Glossary of terms used in Agency technical reports

Agency, the	HSE, acting in its capacity as the GB CLP Agency
AMP	2-amino-2-methylpropan-1-ol
AMP-HCl	2-amino-2-methyl-1-propanol hydrochloride
AR	Applied radioactivity
ATE	Acute toxicity estimate
BCF	Bioconcentration factor
BOD	Biological Oxygen Demand
bw	Body weight
CAR	Competent Authority Report
CAS	Chemical Abstracts Service
CI	Confidence interval
CL	Confidence limits
CLH	Harmonised Classification and Labelling
CLP	Classification, labelling and packaging (of substances and mixtures)
CO_2	Carbon dioxide
COD	Chemical Oxygen Demand
CV	Coefficient of Variation
d	Day
DAR	Draft Assessment Report
DOC	Dissolved Organic Carbon
DS	Dossier Submitter
DT	Dissipation time OR degradation time (also DissT or DegT where apparent)
DT_{50}	Dissipation half-life OR degradation half-life (hours or days), see also above
dw	Dry weight
ECHA	European Chemicals Agency
ECx	x% effect concentration
EFSA	European Food Safety Authority
E_rCx	x% effect concentration based on growth rate
EU	European Union
GCL	Generic concentration limit
GLP	Good Laboratory Practice
H	Hours
HCl	Hydrochloric acid
K_{oc}	Organic carbon-water partition coefficient
K_{ow}	Octanol-water partition coefficient

LC_x	x% lethal effect concentration
MCL	Mandatory Classification and Labelling
M-factor	Multiplying factor
MMAMP	Methylamino-2-methyl-1-propanol
MW	Molecular weight
NOEC	No-observed effect concentration
OECD	Organisation for Economic Co-operation and Development
QSAR	Quantitative structure-activity relationship
RAC	Risk Assessment Committee
RAR	Renewal Assessment Report
RCOM	Response to comments document
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals regulation
SCL	Specific concentration limit
STOT-RE	Specific target organ toxicity – repeated exposure
STOT-SE	Specific target organ toxicity – single exposure
TG	Test Guideline
US EPA	United States Environmental Protection Agency
US DOT	United States Department of Transportation
wt	Weight
wwt	Wet weight

Further information

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