Justification Document for the Selection of a CoRAP Substance

Group Name: Aminophenols

EC	CAS	Substance public name
200-237-1	55-55-0	bis(4-hydroxy-N-methylanilinium) sulphate
202-431-1	95-55-6	2-aminophenol
204-616-2	123-30-8	4-aminophenol
205-768-2	150-75-4	4-methylaminophenol
209-711-2	591-27-5	3-aminophenol
220-618-6	2835-95-2	5-amino-o-cresol
263-847-7	63084-98-0	bis[(4-hydroxyphenyl)ammonium] sulphate
942-297-8	--	reaction mass of 1-naphthol and 4-aminophenol and 3-aminophenol and 5-amino-o-cresol
944-991-6	--	reaction mass of 1-naphthol and resorcinol and 4-aminophenol and 5-amino-o-cresol and 4-amino-m-cresol

Authority: Italy

Date: 18/03/2020

Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update

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1 IDENTITIES OF THE SUBSTANCES WITHIN THE GROUP

1.1 Other identifiers of the substances within the group

EC name (public)	IUPAC name (public)	Index number in Annex VI of the CLP Regulation:	Molecular formula:	Molecular weight or molecular weight range:	Synonyms:
bis(4-hydroxy-N-methylanilinium) sulphate	bis(4-hydroxy-N-methylaniliniu m) sulphate	650-031-00-4	C14H20N2O6S		4-Methylaminophenol sulfate
2-aminophenol	2-aminophenol	612-033-00-3	C6H7NO		
4-aminophenol	4-aminophenol	612-128-00-X	C6H7NO		1-hydroxy-4-aminobenzene
	4-methylaminophenol		C7H9NO		
3-aminophenol	3-aminophenol	612-127-00-4	C6H7NO		1-Hydroxy-3-amino-benzene
5-amino-o-cresol	5-amino-2-methylphenol		C7H9NO		
bis[(4-hydroxyphenyl)ammonium] sulphate	bis[(4-hydroxyphenyl)ammonium] sulphate		C12H16N2O6S		
	Reaction mass of 1-naphthol and 4-aminophenol and 3-aminophenol and 5-amino-o-cresol				
	Reaction mass of 1-naphthol and resorcinol and 4-aminophenol and 5-amino-o-cresol and 4-amino-m-cresol				

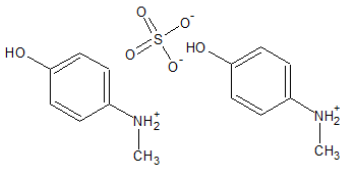
Type of substances

Bis(4-hydroxy-N-methylanilinium) sulphate; 2-aminophenol; 4-aminophenol; 4-methylaminophenol; 3-aminophenol; 5-amino-o-cresol; bis[(4-hydroxyphenyl)ammonium] sulphate.

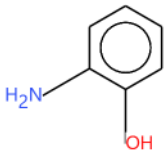
☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formulas

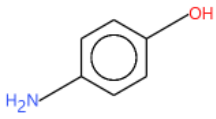
Bis(4-hydroxy-N-methylanilinium) sulphate:



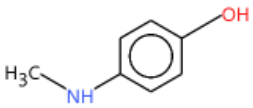
2-aminophenol:



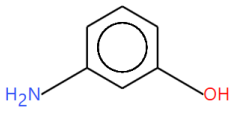
4-aminophenol:



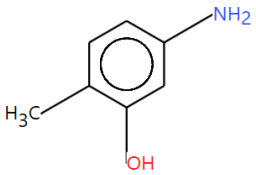
4-methylaminophenol:



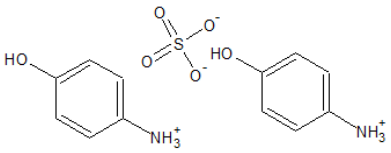
3-aminophenol:



5-amino-o-cresol:



bis[(4-hydroxyphenyl)ammonium] sulphate:

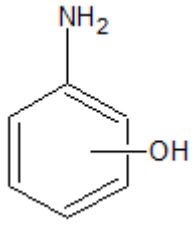


1.2 Similar substances/grouping possibilities

In the shortlist for manual screening round 6, ECHA defined a group of related substances named "aminophenols" consisting of nine members, as reported in table 1.

From this previous group, two reaction mass (reaction mass of 1-naphthol and 4-aminophenol and 3-aminophenol and 5-amino-o-cresol and reaction mass of 1-naphthol and resorcinol and 4-aminophenol and 5-amino-o-cresol and 4-amino-m-cresol) were excluded from the IT CA. These substances were excluded as their evaluation implies the assessment of components (e.g., 1-naphthol and resorcinol) structurally not strictly related with aminophenols. Future evaluation of the two substances (reaction mass), will benefit from the evaluation of the present aminophenols group, which are present as components of the reaction mass. Moreover for these substance no further information are available due the state of non-registered substance, they are only notified to the C&L Inventory substance.

The seven substances left in the group are structurally very similar: they share the same chemical backbone of the aromatic amine, with the hydroxyl substitutent in a different position respect to the amine group (for 2-aminophenol, 3-aminophenol, 4-aminophenol, and its sulphates, the bis[(4-hydroxyphenyl)ammonium] sulphate).



Moreover, three substances carry a methyl group either directly on the aromatic ring (5-amino-o-cresol), or as amino substituent (bis(4-hydroxy-N-methylanilinium) sulphate and 4-methylaminophenol).

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table 1: Completed or ongoing processes

other processes	RMOA	REACH process			Authorisation		Restriction	h C&L	process under other EU legislation		previous legislation		Stockholm convention	other processes EU legislation
EC entries		CCH	TPE	SEV	candidate list	Annex XIV	Annex XVII	Annex VI (CLP)	PPP	BPR	NONS	RAR	POPs	
200-237-1														2012/18/EU (Seveso III)
202-431-1														
204-616-2			TPE concluded											
205-768-2														
209-711-2														
220-618-6														
263-847-7														
942-297-8														
944-991-6														

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

Table 2: Harmonised classification

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
650-031-00-4	bis(4-hydroxy-N-methylanilinium) sulphate	200-237-1	55-55-0	Acute Tox.4* Skin Sens.1 STOT RE 2* Aquatic Acute 1 Aquatic Chronic 1	H302 H317 H373*** H400 H410		
612-033-00-3	2-aminophenol	202-431-1	95-55-6	Acute Tox.4* Acute Tox.4* Muta.2	H302 H332 H341		
612-128-00-X	4-aminophenol	204-616-2	123-30-8	Acute Tox.4* Acute Tox.4* Muta.2 Aquatic Acute 1 Aquatic Chronic 1	H302 H332 H341 H400 H410		
612-127-00-4	3-aminophenol	209-711-2	591-27-5	Acute Tox.4* Acute Tox.4* Aquatic Chronic 2	H302 H332 H411		

3.1.2 Self classification

- In the registration:

bis(4-hydroxy-N-methylanilinium) sulphate:
Acute Tox. 4 H302
STOT Rep. Exp. 2 H373

2-aminophenol:
Acute Tox. 4 H302
Acute Tox.4 H332
Skin Sens. 1A H317

4-aminophenol:
Acute Tox.4 H302
Acute Tox.4 H332
Skin Sens. 1 H317
STOT RE 2 H373

3-aminophenol:
Acute Tox.4 H302
Acute Tox.4 H332
Skin Sens. 1A H317

5-amino-o-cresol:
Skin Sens. 1A H317
Aquatic Chronic 2 H411

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

bis(4-hydroxy-N-methylanilinium) sulphate:
Eye Irrit. 2 H319

2-aminophenol:
Skin Sens. 1 H317

4-methylaminophenol:

Acute Tox. 4	H302
Acute Tox. 4	H332
Muta. 2	H341
Aquatic Chronic 1	H410

3-aminophenol:

Skin Sens. 1	H317
Aquatic Acute 1	H400
Aquatic Chronic 1	H411
Aquatic Chronic 1	H410
STOT RE 2	H373
STOT SE 2	H371

5-amino-o-cresol:

Skin Irrit. 2	H315
Skin Sens. 1	H317
Eye Irrit. 2	H319
STOT SE 3	H335
Aquatic Acute 1	H400
Aquatic Chronic 1	H410
Acute Tox.4	H302
Acute Tox.4	H312

Bis[(4-hydroxyphenyl)ammonium] sulphate:

Acute Tox. 4	H312
Acute Tox. 4	H302
Skin Sens. 1	H317
Eye Dam. 1	H318
Acute Tox. 4	H332
Resp. Sens. 1B	H334
Muta. 2	H341
Aquatic Chronic 1	H410

Reaction mass of 1-naphthol and 4-aminophenol and 3-aminophenol and 5-amino-o-cresol:

Acute Tox. 4	H312
Acute Tox. 4	H302
Skin Sens. 1	H317
Eye Dam. 1	H318
Acute Tox. 4	H332
Resp. Sens. 1B	H334
Muta. 2	H341
Aquatic Chronic 1	H410

Reaction mass of 1-naphthol and resorcinol and 4-aminophenol and 5-amino-o-cresol and 4-amino-m-cresol:

Acute Tox. 4	H312
Acute Tox. 4	H302

Skin Irrit. 2	H315
Skin Sens. 1	H317
Eye Dam. 1	H318
STOT SE 3	H335
Aquatic Acute 1	H400

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

Not applicable.

3.2 Environmental hazard assessment/PBT assessment

Out of the scope of this manual screening.

3.3 Human Health hazard assessment

This assessment is based on the information available in the registration dossiers of the substances belonging to the group of Aminophenols.

There are two substances in this group (EC 205-768-2 and EC 263-847-7) that are not registered and only C&L notifications are available. Another substance (EC 202-431-1), is registered as TII.

Mutagenicity:
4-aminophenol (EC 204-616-2) and 2-aminophenol (EC 202-431-1) have an harmonized classification for Mutagenicity category 2. An in depth evaluation of all the available data and a comparison with CLP criteria for classification as mutagen is necessary to clarify the identified concern for 4-aminophenol (EC 204-616-2).

The data set for mutagenicity of 4-aminophenol (EC 204-616-2) seems to be complete. Negative *in vitro* results were reported in gene mutation (OECD 471) while *in vitro* positive results were reported in mouse lymphoma (OECD 476) and in CA in mammalian cells (OECD 473). Positive *in vivo* results were observed in MN only in CD mice by gavage (OECD 474) while negative results were reported in MN in rats by gavage and no data are available on germ cells. Overall, based on these results a classification of muta cat 2 was assigned to the substance. Due to the widespread use of the substance (consumer use is also reported), a more in deep substance evaluation of the data is needed in order to verify the mutagenicity assigned category or to justify a request of a new study under SEv to refine the classification.

The following three substances of the group (3-aminophenol, EC 209-711-2; bis(4-hydroxy-N-methyl anilinium) sulphate, EC 200-237-1); 5-amino-o-cresol (EC 220-618-6) have not a classification as mutagen.
For the 3-aminophenol (EC 209-711-2) negative results were reported in an *in vitro* bacterial and mammalian gene mutation (OECD 471, OECD 476) while mixed results were reported in MN (OECD 473). Only one study is available for *in vivo* follow-up (MN *in vivo* in rats by gavage) with no clear indication on target organ exposure.
For bis(4-hydroxy-N-methyl anilinium) sulphate (EC 200-237-1), positive *in vitro* results were observed in bacterial gene mutation assay while negative results were observed in mammalian gene mutation assay. The *in vivo* results showed negative results in an *in vivo* MN tests in rats by gavage. In this assay, there is no indication of toxicity to bone marraw (the ratio PCE/NCE was not lower in all treated groups than in the negative control group).

A complex picture is available for 5-amino-o-cresol (EC 220-618-6) with the following *in vitro* results: negative in bacterial gene mutation and positive in mammalian cells both for gene mutation and chromosomal aberration while mixed results were reported for micronucleus assay in mammalian cell lines. A complex picture is available for the *in vivo* results that can be summarized as follow: negative results were reported in micronucleus *in vivo* in mice by i.p. and in rats by gavage (in all studies no indication of target organ toxicity is available), negative results were also reported in the UDS in rats by gavage and in a very old dominant leathal study, ambiguous results were reported in a comet assay performed in the liver cells while negative results were observed in stomach and urinary bladder epithelium cells in rats by gavage.

Overall, it can be concluded that the mutagenicity concern need to be addressed for the four registered substances of the group.

Repeated dose toxicity
All the group members for which data are submitted, show STOT RE potential.

Regarding the substance bis(4-hydroxy-N-methylanilinium) sulphate (EC 200-237-1) the data submitted in the registration dossier confirm the STOT RE classification. Based on (Q)SAR predictions and the experimental data available for the target chemical, N-Methyl-paminophenl sulfate is likely to exhibit a toxic nature upon repeated exposure by oral route.
Regarding the substance 2-aminophenol (EC 202-431-1), in the registration dossier two subacute oral toxicity studies in rats were submitted with 2-aminophenol. In study 1 with treatment over 30 days at daily doses 0, 20, 80, 320 mg/kg bw, none of the three tested doses could be considered as a NOAEL. In study 2 with doses of 0, 2. 5 and 15 mg/kg bw/d, a NOAEL of 5 mg/kg bw/d was derived based on the thyroid weight changes observed.

For the substance 4-aminophenol (EC 204-616-2) two studies have been submitted in the registration dossier: a subchronic study (90 days) conducted according to GLP and OECD guideline 408 in the rat with a NOAEL of 10 mg/kg bw/day and a LOAEL of 30 mg/kg bw/day and a subacute toxicity study (28-day) conducted according to GLP and OECD guideline 407 in the rat with a NOAEL of 20 mg/kg bw/day. The NOAEL from the 90-day study was used by the registrant to calculate the DNEL, long-term inhalation route systemic and DNEL, long term dermal route systemic. The primary target organ of toxicity in the 28-day study and 90-day study was the kidney.

For the substance 3-aminophenol (EC 209-711-2) several studies have been submitted in the registration dossier. In the oral studies female rats were administered the material daily by gavage at the concentrations of 0, 20, 70, 200 or 600 mg/kg/day for 13 weeks. At 70 mg/kg/day, a dose related thyroid hyperactivity and the presence of the test substance in the renal tubules were found. At 200 mg/kg/day, marked haemosiderosis was noted in the spleen and blood biochemical parameters were disturbed. At 600 mg/kg/day, signs of marked clinical, haematological, biochemical and histopathological toxicity were observed. No toxic effects were observed at 20 mg/kg/day. Therefore, NOEL was considered to be 20 mg/kg/day when female Sprague-Dawley Crl CD (SD) BR rats were exposed to the test material on a daily basis for 13 weeks.
The dermal studies submitted are poorly reported being from peer reviewed so an evalutation of the effects after dermal repeated exposure could not be drawn.
The 5-amino-o-cresol (EC 220-618-6) the following studies have been submitted. A first study was performed with similar OECD guideline 408. Males and females rats were treated daily by oral gavage with the registered test item. Doses used were 0, 300, 900 and 2700 mg/kg bw/day. The main toxic effects in this study were local irritation on the stomach mucosa, hepatotoxicity and toxic effects on the

red blood cells, and a transient effects on the general behaviour immediately after application in the beginning of the study. Although of less severity, some of these effects were observed at the lowest dose level. Hence, particularly due to the effect observed at the low dose level (organ weight changes), no NOAEL can be derived. The LOAEL was defined as 300 mg/kg bw/day.
A secondary gavage study during 90 days with the same method was performed at lowest doses to investigate a non-effect dose. This study focused on three effects observed in the precedent assay: (1)disturbed general condition with central nervous symproms immediately after the administration (2) decrease in the number of red blood cells (decrease of hematocrit) and (3) increased relative liver weight. No toxicity was observed during the treatment period at all the tested doses. The NOAEL (No observed adverse effect level) was defined as 180 mg/kg bw/day.
One relevant *in vivo* study was performed in order to evaluate the potential toxicity of the registered substance during repeated exposure by oral route (feeding studies). Sprague Dawley rats were exposed continuously to test item mixed in diet at 0.21% in diet (equivalent to 180.9 and 205.88 mg/kg bw/day in males and females respectively), 0.95% in diet (equivalent to 818.35 and 931.37 mg/kg bw/day in males and females respectively) and 2.95% in diet equivalent to 2541.2 and 2892.16 mg/kg bw/day in males and females respectively). They were exposed for 90 days. In this study, with the exception of visibly enlarged thyroids in the animals treated with 1.0 and 3.0%, there were no consistent external or internal abnormalities or gross lesions observed in treated animals that could be related to treatment. Microscopic examination of the organs revealed test material dose related changes in the thyroid glands in the animals treated at all dose levels. The changes noted were a combination of mild to moderate follicular cell hyperplasia, misshapen follicles, and small follicles. The appearance of these glands was similar to that of a "sporadic microfollicular goiter". This effect is caused by an increase in the cell size of the columnar epithelium surrounding the follicles in the thyroid. Centrilobular hepatocytomegaly was noted in livers of several test animals (1 male and 1 female at the low dose, 2 males at mid dose and in 4 males and 3 females in the high dose group) and may reflect the site of metabolism of the drug. The few changes in other tissues were distributed among test and control rats and were considered spontaneous incidental lesions.

No conclusion on the STOT RE potential of 4-methylaminophenol (EC 205-768-2) and Bis[(4-hydroxyphenyl)ammonium] sulphate (EC 263-847-7) could be drawn, beeing these substances not registered.
Overall, it can be concluded that the STOT RE concern need to be addressed for all the group's substances.

Skin sensitisation
All the group members for which data are submitted, show skin sensitisation potential.
The substance bis(4-hydroxy-N-methylanilinium) sulphate (EC 200-237-1) has an harmonized classification as Skin Sens.1 H317. The data submitted in the registration dossier does not allow a sub-categorization due to the high concentration used in the LLNA and Guinea pig studies. Also studies on humans indicate that at least the sub-categorization in 1B can be made. Neverthless, a more in-depth assessment of the effects of skin sensitization by studies with appropriate concentrations could allow to sub-categorize the substance in the relevant hazard class. Also for the substance 4-aminophenol (EC 204-616-2), as for bis (4-hydroxy-N-methylanilinium) sulphate, the study submitted (Guinea Pig) does not allow a sub-categorization and a more in-depth assessment of the effects of skin sensitization by studies with appropriate concentrations could allow to sub-categorize the substance in the relevant hazard class.

Regarding 3-aminophenol (EC 209-711-2) and 5-amino-o-cresol (EC 220-618-6) the data submitted in the registration dossier confirm the sensitizer potential and are supportive of the self classification as Skin Sens. 1A H317.
No conclusion on the sensitising potential of 4-methylaminophenol (EC 205-768-2) and Bis[(4-hydroxyphenyl)ammonium] sulphate (EC 263-847-7) could be drawn, beeing these substances not registered. Overall, it can be concluded that the sensitising concern need to be addressed for all the group's substances.

Table 3: Overview of toxicological data

Toxicological endpoints	bis(4-hydroxy-N-methylanilinium) sulphate *EC* 200-237-1	2-aminophenol *EC* 202-431-1	4-aminophenol *EC* 204-616-2	4-methylaminophenol *EC 205-768-2*	bis[(4-hydroxyphenyl)ammonium] sulphate *EC 263-847-7*	3-aminophenol *EC 209-711-2*	5-amino-o-cresol *EC 220-618-6*
Oral acute toxicity, LD50 (mg/kg bw) in rats	1578.59 (Data is from OECD QSAR toolbox v3.3)	2500 (OECD 401)	671 (OECD 401)			2000 (OECD 423)	3600 Pre-GLP no guideline (standard acute method followed)
Inhalation acute toxicity, LC50 (mg/L) in rats	Waiver		3.42 (equivalent or similar to OECD Guideline 403)			1162 (data from handbook or collection of data)	42570 No guideline followed: extrapolation calculation from the oral study
Dermal acute toxicity, LD50 (mg/kg bw) in rabbit	7187.2 (Data is from OECD QSAR toolbox v3.3)		8000 (equivalent or similar to EPA OPPTS 870.1200)			8112 (data from handbook or collection of data)	5688 No guideline followed: extrapolation calculation from the oral study
Skin irritation	Not irritant (OECD 404)	Not irritant (US Code of Fed Reg 16, Sec 1500.41)	Not irritant (equivalent or similar to OECD Guideline 404)			Not irritant (OECD 404)	Not irritant (OECD guideline method 439 and 431)
Eye irritation	Not irritant (OECD 405)	Not irritant (OECD 492)	Not irritant (equivalent or similar to EPA OPPTS 870.2400)			Not irritant (OECD 405	Not irritant (OECD guidelines 438 and 492 methods)
Skin sensitisation	Sensitizer (data from handbook or collection of data; LLNA and GPMT)	Sensitizer (OECD 442C)	Sensitizer (OECD 406; GPMT)			Sensitizer (OECD 429)	Sensitizer (OECD 429)
Repeated dose toxicity, NOAEL (mg/kg bw/d) in rats	Oral: 56.91 (OECD QSAR toolbox version 3.3), Inhalation: waiver Dermal: 11.47 (Data is from peer reviewed publication)	Oral: 5 (OECD 407)	10 (OECD 408)			20 (Data is from study report) Dermal LOAEL: 500 (Data is from study report)	Oral: 180 (OECD 408)
Mutagenicity *in vitro*	Positive (in TA100 and TA1537 +S9) (OECD 471) Negative in mouse lynphoma (OECD 476)	Positive (in TA 100) (OECD 471) Negative in UDS in vitro (no GL) Negative in CA (no GL)	Negative (OECD 471) Positive in mouse lynphoma (OECD 476)			Negative (OECD 471) Negative (OECD 476) Mixed results (OECD 473)	Negative (OECD 471) Positive (OECD 476) Positive in human lynphocites (OECD 473)

Toxicological endpoints		bis(4-hydroxy-N-methylanilinium) sulphate *EC* 200-237-1	2-aminophenol *EC* 202-431-1	4-aminophenol *EC* 204-616-2	4-methylaminophenol *EC 205-768-2*	bis[(4-hydroxyphenyl)ammonium] sulphate *EC 263-847-7*	3-aminophenol *EC 209-711-2*	5-amino-o-cresol *EC 220-618-6*
				Positive in CA in mammalian cells (OECD 473)				Mixed results in MN in vitro (OECD 487)
Mutagenicity *in vivo*		Negative in MN in rats by gavage (OECD 474) Negative in UDS in rats by gavage (OECD 486)	Positive in *vivo* germ cells (no GL) Negative *in vivo* MN (no GL)	Positive in CD mice by gavage (OECD 474) Negative in rats by gavage (OECD 474)			Negative in rats (OECD 474)	Negative in mice by gavage (OECD 474) Negative in mice by I.P. (OECD 474) Negative in rats by gavage (OECD 474) Negative in rats by gavage (OECD 486) Negative in DL in rats (OECD 478) Ambiguos results in liver and negative results in stomach and urinary bladder epithelium cells in rats by gavage (OECD 489)
Toxicity to reproduction, NOAEL/NOEL (mg/kg bw/d) in rats	**F**	NOAEL P (systemic oral route) = 740 NOAEL P (systemic dermall route) = 11.47 NOAEL F1 = 11.47 Prediction was done using OECD QSAR toolbox v3.3, 2017:		NOAEL repro = 20 (OECD 421)			NOAEL: 10 LOAEL P (systemic) = 25 NOAEL repro = 10 NOAEL F1 = 10 90 days feeding study followed by teratology study	NOAEL P (systemic) = 200 NOAEL repro = 200 NOAEL F1 = 200 (OECD 422)
	D	LOEL maternal = 25 NOAEL dev = 125 (OECD 414)	NOAEL maternal = 70 NOAEL dev = 70 (OECD 414)	NOEL maternal = 20 NOAEL dev = 100 (OECD 421)			NOAEL maternal = 30 NOAEL dev = 100 (OECD 414)	NOAEL maternal = 180 NOAEL dev = 180 (OECD 414)

3.3.1 *In silico* screening

OECD QSAR Toolbox v4.3 was used for the *in silico* screening of the seven substances left in the group. Concerning the two sulphates (EC 200-237-1 and EC 263-847-7), both the ionic and the neutral forms were included in the analysis. The results of the profilers used should be not considered as a prediction but as a decision supporting tool.

The following profilers for each endpoint were used:

- Skin Sensitisation: Keratinocyte gene expression, Protein binding alerts for skin sensitization according to GHS, Protein binding for skin sensitization by OASIS, Protein Binding Potency h-CLAT, Protein binding by OASIS, Protein binding by OECD, Protein binding potency Cys (DPRA 13%), Protein binding potency GSH, Protein binding potency Lys (DPRA 13%).

- Repeated dose toxicity: HESS.

- Genotoxicity: DNA alerts for AMES by OASIS, DNA alerts for CA and MNT by OASIS; *in vitro* mutagenicity (Ames test) alerts by ISS, in vivo mutagenicity (Micronucleus) alerts by ISS, Protein binding alerts for Chromosomal aberration by OASIS.

Skin sensitization

Among the profilers relevant for skin sensitization, available in OECD QSAR Toolbox v4.3, all the group members trigger either the Keratinocyte gene expression profiler, or the protein binding potency GSH. The results for the *in silico* skin sensitization screening are reported in Table 4. Profilers with negative results for all the substances are omitted.

Table 4: *in silico* profiling results for skin sensitization (OECD QSAR Toolbox v4.3). NA= No alert found

EC/List No	Name	Keratinocyte gene expression	Protein binding potency GSH
200-237-1	Bis(4-hydroxy-N-methylanilinium) sulphate	Substituted para- and ortho-phenylenediamines, aminophenols and benzenediols (Very high gene expression)	NA
202-431-1	2-aminophenol	Substituted para- and ortho-phenylenediamines, aminophenols and benzenediols (Very high gene expression)	NA
204-616-2	4-aminophenol	Substituted para- and ortho-phenylenediamines, aminophenols and benzenediols (Very high gene expression)	NA
205-768-2	4-methylaminophenol	Substituted para- and ortho-phenylenediamines, aminophenols and benzenediols (Very high gene expression)	NA
209-711-2	3-aminophenol	NA	Suspect (GSH) (Acid-Base reaction - non

			covalent interaction)
220-618-6	5-amino-o-cresol	Substituted para- and ortho-phenylenediamines, aminophenols and benzenediols (Very high gene expression)	Suspect (GSH) (Acid-Base reaction - non covalent interaction)
263-847-7	Bis[(4-hydroxyphenyl)ammonium] sulphate	Substituted para- and ortho-phenylenediamines, aminophenols and benzenediols (Very high gene expression)	NA

Repeated dose toxicity

The *in silico* screening for the Repeated dose toxicity was performed by HESS profiler, as implemented in the Toolbox. Table 6 shows the results for this profiler.

Table 5: *in silico* profiling results for Repeated dose toxicity (OECD QSAR Toolbox v4.3).

EC/List No	Name	Repeated dose (HESS) profiler
200-237-1	Bis(4-hydroxy-N-methylanilinium) sulphate	Dapsone (dia minodiphenyl sulfone, DDS) (Renal Toxicity Alert) o-/p-Aminophenols (Hemolytic anemia with methemoglobinemia) Rank B Oxyphenisatin (Hepatotoxicity) Alert
202-431-1	2-aminophenol	o-/p-Aminophenols (Hemolytic anemia with methemoglobinemia) Rank B Styrene (Renal Toxicity) Alert Toluene (Renal toxicity) Alert
204-616-2	4-aminophenol	Acetaminophen (Hepatotoxicity) Alert Acetaminophen (Renal toxicity) Alert o-/ p-Aminophenols (Hemolytic anemia with methemoglobinemia) Rank B p-Aminophenols (Renal toxicity) Rank B
205-768-2	4-methylaminophenol	Acetaminophen (Hepatotoxicity) Alert Acetaminophen (Renal toxicity) Alert
209-711-2	3-aminophenol	Not categorized
220-618-6	5-amino-o-cresol	Not categorized
263-847-7	Bis[(4-hydroxyphenyl)ammonium] sulphate	Dapsone (dia minodiphenyl sulfone, DDS) (Renal Toxicity) Alert o-/ p-Aminophenols (Hemolytic anemia with methemoglobinemia) Rank B Oxyphenisatin (Hepatotoxicity) Alert

Genotoxicity

All the group members trigger an alert of at least one *endpoint specific* profiler, relevant for genetic toxicity. The results for *in silico* genotoxicity screening are reported in Table 6. Profilers with negative results for all the substances are omitted.

Considering the hypothesized mechanisms of action and the structural-activity relationionships of the group's substances, it can be concluded that the mutagenicity concern need to be addressed thoroughly.

Table 6: *in silico* profiling results for genotoxicity (OECD QSAR Toolbox v4.3). NA= No alert found

EC/List No	Name	DNA alerts for CA and MNT by OASIS	in vitro / in vivo mutagenicity alerts by ISS	Protein binding alerts for Chromosomal aberration by OASIS
200-237-1	Bis(4-hydroxy-N-methylanilinium) sulphate	NA	Aromatic mono- and dialkylamines	Substituted Anilines
202-431-1	2-aminophenol	Single-Ring Substituted Primary Aromatic Amines	Primary aromatic amines, hydroxyl amines and derived esters	Substituted Anilines
204-616-2	4-aminophenol	Single-Ring Substituted Primary Aromatic Amines	Primary aromatic amines, hydroxyl amines and derived esters	Substituted Anilines
205-768-2	4-methylaminophenol	NA	Aromatic mono- and dialkylamines	NA
209-711-2	3-aminophenol	Single-Ring Substituted Primary Aromatic Amines	Primary aromatic amines, hydroxyl amines and derived esters	Substituted Anilines
220-618-6	5-amino-o-cresol	NA	Primary aromatic amines, hydroxyl amines and derived esters	Substituted Anilines
263-847-7	Bis[(4-hydroxyphenyl)ammonium] sulphate	NA	Primary aromatic amines, hydroxyl amines and derived esters	Substituted Anilines

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES

4.1 Tonnage and registration status*

Information based on content of registration dossier and dissemination website dated 14 June 2019 and thus not taking into account any dossier update after that date.

Table 7: Tonnage and registration status *

From ECHA dissemination site Bis(4-hydroxy-N-methylanilinium) sulphate (EC 200-237-1)		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☒ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

From ECHA dissemination site 2-aminophenol (EC 202-431-1)		
☐ Full registration(s) (Art. 10)	☒ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

From ECHA dissemination site 4-aminophenol (EC 204-616-2)		
☒ Full registration(s) (Art. 10)	☒ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☒ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

From ECHA dissemination site 3-aminophenol (EC 209-711-2)		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☒ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

From ECHA dissemination site 5-amino-o-cresol (EC 220-618-6)		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☒ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

*****the total tonnage band has been calculated by excluding the intermediate uses, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11):

https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0

4.2 Overview of uses

Substance: Bis(4-hydroxy-N-methylanilinium) sulphate (EC 200-237-1)						
☐ Manufacture	☐ Formulation	☒ Industrial use	☒ Professional use	☐ Consumer use	☐ Article service life	☐ Closed system
Substance: 2-aminophenol (EC 202-431-1)						
☐ Manufacture	☐ Formulation	☒ Industrial use	☐ Professional use	☐ Consumer use	☐ Article service life	☐ Closed system
Substance: 4-aminophenol (EC 204-616-2)						
☒ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☐ Closed system
Substance: 3-aminophenol (EC 209-711-2)						
☐ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☐ Closed system
Substance: 5-amino-o-cresol (EC 220-618-6)						
☐ Manufacture	☒ Formulation	☐ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☐ Closed system

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE OR GROUP

5.1. Legal basis for the proposal

☒ Article 44(2)

☐ Article 45(5)

5.2. Selection criteria met (why the substance or group qualifies for being in CoRAP)

☒ Fulfils criteria as CMR/ Suspected CMR

☒ Fulfils criteria as Sensitiser/ Suspected sensitiser

☐ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☐ Fulfils criteria high (aggregated) tonnage

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

☐ Fulfils risk criteria

According to the registration dossiers, 2-aminophenol (EC 202-431-1) is only used under strictly controlled conditions. Bis(4-hydroxy-N-methylanilinium) sulphate (EC 200-237-1) is registered for 1-10 tpa and no consumer uses are reported. It is included nevertheless as it may serve as substitute in case the hazard profile may come out favourable compare to the alternatives.

5.3 Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☒ M ☐ R	☒ Sensitiser	☒ Other (please specify below)
☐ PBT/vPvB	☐ Potential endocrine disruptor	

Exposure/risk based concerns		
☐ Consumer use	☐ Exposure of workers	☐ Other (please specify below)
☐ Exposure of sensitive populations	☐ Exposure of environment	

Mutagenicity:

The substance of the group for which is envisaged a Substance Evaluation are the following:

- 4-aminophenol (EC 204-616-2),
- 3-aminophenol, (EC 209-711-2);
- bis(4-hydroxy-N-methyl anilinium) sulphate (EC 200-237-1)
- 5-amino-o-cresol (EC 220-618-6)

4-aminophenol (EC 204-616-2) has an harmonized classification for Mutagenicity category 2. An in deep evaluation of all the available data and a comparison with CLP criteria for classification as mutagen is necessary to clarify the identified concern.

The data set for mutagenicity of 4-aminophenol (EC 204-616-2) seems to be complete. Negative *in vitro* results were reported in gene mutation (OECD 471) while *in vitro* positive results were reported in mouse lymphoma (OECD 476) and in CA in mammalian cells (OECD 473). Positive *in vivo* results were observed in MN only in CD mice by gavage (OECD 474) while negative results were reported in MN in rats by gavage and no data are available on germ cells. Overall, based on these results a classification of muta cat 2 was assigned to the substance. Due to the widespread use of the substance (consumer use is also reported), a more in depth substance evaluation of the data is needed in order to verify the mutagenicity assigned category or to justify a request of a new study under SEv to refine the classification.

The following three substances of the group (3-aminophenol, EC 209-711-2; bis(4-hydroxy-N-methyl anilinium) sulphate, EC 200-237-1); 5-amino-o-cresol (EC 220-618-6) have not a classification as mutagen.

For the 3-aminophenol (EC 209-711-2) negative results were reported in an *in vitro* bacterial and mammalian gene mutation (OECD 471, OECD 476) while mixed results were reported in MN (OECD 473). Only one study is available for *in vivo* follow-up (MN *in vivo* in rats by gavage) with no clear indication on target organ exposure.

For bis(4-hydroxy-N-methyl anilinium) sulphate (EC 200-237-1), positive *in vitro* results were observed in bacterial gene mutation assay while negative results were observed in mammalian gene mutation assay. The *in vivo* results showed negative results in an *in vivo* MN tests in rats by gavage. In this assay, there is no indication of toxicity to bone marraw (the ratio PCE/NCE was not lower in all treated groups than in the negative control group).

A complex picture is available for 5-amino-o-cresol (EC 220-618-6) with the following *in vitro* results: negative in bacterial gene mutation and positive in mammalian cells both for gene mutation and chromosomal aberration while mixed results were reported for micronucleus assay in mammalian cell lines. A complex picture is available for the *in vivo* results that can be summarized as follow: negative results were reported in micronucleus *in vivo* in mice by i.p. and in rats by gavage (in all studies no indication of target organ toxicity is available), negative results were also reported in the UDS in rats by gavage and in a very old dominant leathal study, ambiguous results were reported in a comet assay performed in the liver cells while negative results were observed in stomach and urinary bladder epithelium cells in rats by gavage.

Moreover the *in silico* screening by the OECD QSAR Toolbox (v4.3) showed that all the group members trigger an alert in at least one endpoint specific profiler, relevant for genetic toxicity.
Overall, it can be concluded that the mutagenicity concern need to be addressed for the four registered substances of the group.

Systemic toxicity:
All the group members for which data are submitted, show STOT RE potential.
The substance bis(4-hydroxy-N-methylanilinium) sulphate (EC 200-237-1) is already classified as STOT RE and the data submitted in the registration dossier confirm the harmonized classification.
Regarding the substance 2-aminophenol (EC 202-431-1), in the registration dossier two subacute oral toxicity studies in rats were submitted. In study 1 with treatment over 30 days at daily doses 0, 20, 80, 320 mg/kg bw, none of the three tested doses could be considered as a NOAEL as the effects were observed even in the low dose. In study 2 with doses of 0, 2, 5 and 15 mg/kg bw/d, a NOAEL of 5 mg/kg bw/d was derived based on the thyroid weight changes observed.
For the substance 4-aminophenol (EC 204-616-2) two studies have been submitted in the registration dossier: a subchronic study (90 days) conducted according to GLP and OECD guideline in the rat with a NOAEL of 10 mg/kg bw/day and a LOAEL of 30 mg/kg bw/day and a subacute toxicity study (28-day) conducted according to GLP and per OECD guideline in the rat with a NOAEL of 20 mg/kg bw/day. The NOAEL from the 90-day study was used by the registrant to calculate the DNEL, long-term inhalation route systemic and DNEL, long term dermal route systemic. The primary target organ of toxicity in the 28-day study and 90-day study was the kidney.
For the substance 3-aminophenol (EC 209-711-2) several studies have been submitted in the registration dossier. In the oral studies female rats were administered the material daily by gavage at the concentrations of 0, 20, 70, 200 or 600 mg/kg/day for 13 weeks. At 70 mg/kg/day, a dose related thyroid hyperactivity and the presence of the test substance in the renal tubules were found. At 200 mg/kg/day, marked haemosiderosis was noted in the spleen and blood biochemical parameters were disturbed. At 600 mg/kg/day, signs of marked clinical, haematological, biochemical and histopathological toxicity were observed. No toxic effects were observed at 20 mg/kg/day. Therefore, NOEL was considered to be 20 mg/kg/day when female Sprague-Dawley Crl CD (SD) BR rats were exposed to the test material on a daily basis for 13 weeks.
The 5-amino-o-cresol (EC 220-618-6) the following studies have been submitted. A first study was performed with similar OECD guideline 408. Males and females rats were treated daily by oral gavage with the registered test item. Doses used were 0, 300, 900 and 2700 mg/kg bw/day. The main toxic effects in this study were local irritation on the stomach mucosa, hepatotoxicity and toxic effects on the red blood cells, and a transient effects on the general behaviour immediately after application in the beginning of the study. Although of less severity, some of these effects were observed at the lowest dose level. Hence, particularly due to the effect observed at the low dose level (organ weight changes), no NOAEL can be derived. The LOAEL was defined as 300 mg/kg bw/day.
A secondary gavage study during 90 days with the same method was performed at lowest doses to investigate a non-effect dose. This study focused on three effects observed in the precedent assay: (1) disturbed general condition with central nervous symproms immediately after the administration (2) decrease in the number of red blood cells (decrease of hematocrit) and (3) increased relative liver weight. No toxicity was observed during the treatment period at all the tested doses. The NOAEL (No observed adverse effect level) was defined as 180 mg/kg bw/day.
One relevant *in vivo* study was performed in order to evaluate the potential toxicity of the registered substance during repeated exposure by oral route (feeding studies). Sprague Dawley rats were exposed continuously to test item mixed in diet at 0.21% in diet (equivalent to 180.9 and 205.88 mg/kg bw/day in males and females respectively), 0.95% in diet (equivalent to 818.35 and 931.37 mg/kg bw/day in males and females respectively) and 2.95% in diet equivalent to 2541.2 and 2892.16 mg/kg bw/day in males and females respectively). They were exposed for 90 days. In this study, with the exception of visibly enlarged thyroids in the animals treated with 1.0 and 3.0%, there were no consistent external or internal abnormalities or gross lesions observed in treated animals that could be related to treatment. Microscopic examination of the organs revealed test material dose related changes in the thyroid glands in the animals

treated at all dose levels. The changes noted were a combination of mild to moderate follicular cell hyperplasia, misshapen follicles, and small follicles. The appearance of these glands was similar to that of a "sporadic microfollicular goiter". This effect is caused by an increase in the cell size of the columnar epithelium surrounding the follicles in the thyroid. Centrilobular hepatocytomegaly was noted in livers of several test animals (1 male and 1 female at the low dose, 2 males at mid dose and in 4 males and 3 females in the high dose group) and may reflect the site of metabolism of the drug.

These findings raise concern that the substances not already classified under CLP might be toxicants after repeated exposure, some of them with a suspect ED mechanism. Thus, an in depth evaluation is necessary to clarify the initial concern regarding the STOT RE potential for all the substances of the group.

Skin sensitisation

All the group members for which data are submitted, show skin sensitisation potential.
The substance bis(4-hydroxy-N-methylanilinium) sulphate (EC 200-237-1) has an harmonized classification as Skin Sens.1 H317. The data submitted in the registration dossier does not allow a sub-categorization due to the high concentration used in the LLNA and Guinea pig studies. Also studies on humans indicate that at least the sub-categorization in 1B can be made. Neverthless, a more in-depth assessment of the effects of skin sensitization by studies with appropriate concentrations could allow to sub-categorize the substance in the relevant hazard class. Also for the substance 4-aminophenol (EC 204-616-2), as for bis (4-hydroxy-N-methylanilinium) sulphate, the study submitted (Guinea Pig) does not allow a sub-categorization and a more in-depth assessment of the effects of skin sensitization by studies with appropriate concentrations could allow to sub-categorize the substance in the relevant hazard class.

Regarding 3-aminophenol (EC 209-711-2) and 5-amino-o-cresol (EC 220-618-6) the data submitted in the registration dossier confirm the sensitizer potential and are supportive of the self classification as Skin Sens. 1A H317.

5.4 Preliminary indication of information that may need to be requested t clarify the concern

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☒ Information on ED potential	☐ Other (provide further details below)

5.5 Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☐ Authorisation	☐ Other (provide further details)
Harmonised C&L might follow, depending upon the outcome of the evaluation.			