Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at Community level of

amines, tallow alkyl

ECHA/RAC/CLH-O-0000002199-69-01/A2

Adopted

2 December 2011

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: amines, tallow alkyl
CAS number: 61790-33-8
EC number: -
General comments

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	Thank you for the considerable work that has gone into writing these proposals. We agree with the category and read-across approach used, but we have comments on the proposal which are detailed below. The aim of an Annex VI proposal is to determine the classification and labelling of a substance. We note, in several sections, an opinion has been given as to whether further testing is required. As the classification decision is based on available data, we do not feel these statements are relevant and suggest they are removed.	DE: Thank you. We noticed that only statements were made that no further testing was required; these statements – while certainly not strictly necessary for the CLH proposal – were left in the text to underscore the fact that the existing database was regarded as complete.	We agree with UK comments, the statements are inconsistent with CLP requirements.
03/12/2010	Sweden / Ing-Marie Olsson / Member State	Sweden supports the proposed classification of Amines, tallow alkyl (CAS No 61790-33-8) as specified in the proposal. Sweden agrees with the rationale for classification into the proposed hazard classes and differentiations	DE: Thank you.	No additional comments
03/12/2010	Portugal Maria do Carmo / Portuguese Environment Agency / National Authority	Considering the present proposal, we agree to establish an harmonised classification & labelling for amines, tallow alkyl. The proposed Classification and Labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive(environment).Therefore, we support the proposal.	DE: Thank you.	No additional comments

03/12/2010	Ireland / Health & Safety Authority / Member State	Human Health: The Irish CA is in agreement with the proposed classification for human health: Xn, C; R22, R35, R37, R48/22 (Directive 67/548/EEC) and Acute Tox 4, H302; Skin Corr 1A, H314; STOT SE 3, H335; STOT RE 2, H373 (CLP Regulation). Environment: The Irish CA is in agreement with the proposed environment classification, as previously agreed at the TC C&L 09 of 2005 and subsequently confirmed at the TC C&L 04 of 2006.	DE: Thank you.	We agree with DE
02/12/2010	Germany / APAG Primary Fatty Amine Consortium / Industry or trade association	*ECHA has copied the comments below from the attachment (CLH_Dossier-Comments_Tallow.pdf).* Dear Sirs, Over the last 10 years a risk assessment under the existing substance regulation 93/793/EC for five primary alkyl amines was carried out by the authorities (MSCA = Germany). Based on the data available at that time the following classification & labelling for the environment was proposed by the MSCA for the five primary fatty amines: • N, R 50/R53 Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment. For the human health part, the risk assessment process was formally not finalized within the transition period concerning the implementation of Regulation (EC) 1907/2006 (REACH). Thus, the MSCA published transitional dossiers, while industry prepared registration dossiers following REACH Guidance. During dossier preparation by industry significant new data were generated, e.g. phys-chem properties, bioconcentration factor, etc. allowing more detailed evaluations of the substances under concern. Consequently the transitional dossiers prepared by the MSCA and the newly generated data were taken into account by Industry for the preparation of the registration dossiers and the CSR. According to ECHA-Guidance on substance identification the registration of all five primary alkyl amines was performed using the following nomenclature: • C12-18-(even numbered)-alkylamines (CAS-No. = 68155-27-1) Synonym for Amines, Coco alkyl (CASNo. = 61788-46-3) • C16-18-(even numbered) -alkylamines (CAS-No. = 90640-32-7) Synonym for Amines, hydrogenated tallow alkyl (CAS-No. = 61788-45-2) • C16-18-(even numbered, C18-unsaturated)-alkylamines (CAS-No. = 68037-95-6) Synonym for Amines, tallow alkyl (CAS-No. = 61790-33-8) • C16-18-(even numbered, saturated and unsaturated)-alkylamines (CAS-No. = 1213789-63-9) Synonym for (Z)-octadec-9-enylamine (CAS-No. = 112-90-3) • Octadecylamine (CAS-No. = 124-30-1) Industrys (Registrants) common conclusion based on the new data available concerning the environment / ecotoxicity also with respect to the new CLP-regulation provided as part of the joint submission is as follows: • N, R 50 Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment. • Acute (short-term) aquatic hazard, Acute category 1 H400: Very toxic to aquatic life (M-factor = 10) With regard to human health, the proposed classification and labelling in the CLH dossiers are not in line with the respective classification & labelling discussed and agreed at TCNES level according to the former existing substances regulation 93/793/EEC. In the mean time - **after** the Reach Dossiers were submitted by Industry (Registrants) - the MSCA prepared and published through ECHA CLH-Dossiers for the above mentioned five primary alkyl amines, based solely on the data available in the transitional dossiers only, not taking into account the additional data provided in the Reach	DE: Because of the limited space in the 'Response' column the extensive comments by APAG are addressed in an appendix to this RCOM table (Appendix 2).	We address our responses in Appendix 3

		Dossiers submitted. Additionally, Industry (Registrants) would like to point out that all members of the consortia taking part in the registration had come to a common classification and labelling (self-classification) of the five primary alkylamines under consideration. In this respect, Industry is wondering about the action of the MSCA to request a common harmonization of the classification and labelling at EU community level which in our opinion is unjustified. Please find included our comments on the CLH-Dossiers for above mentioned substances. Sincerely Yours On behalf of APAG-Primary Fatty Amines Consortium **CLH-DOSSIER** **Comments on Amines, tallow alkyl** **[Cas-No. = 61790-33-8, EC-No. = 263-125-1]** **REACH-Registration No. (Clariant) XX-XXXXXXXXXX-XX-XXXX1** **Introduction** In January 2010 the MSCA published transitional dossiers, while Industry prepared registration dossiers following REACH Guidance. During dossier preparation by industry with Clariant being the lead registrant, essential new data were generated, like e.g. physico-chemical properties, bioconcentration factor, etc. Consequently the transitional dossiers prepared by the MSCA and the newly generated data were taken into account by Industry for the preparation of the registration dossiers and the CSR. This resulted in the successful registration of all five primary alkyl amines following ECHA-Guidance on substance identification (for Registration No. 1 see table below):		

	Name used in EU Risk Assessment ESR 93/793/EEC	Name to be used for REACH Registration under 2006/1907/EC
Chemical Name	Amines, Coco alkyl	C12-18-(even numbered)-alkylamines
EC Number	262-977-1	268-953-7
CAS Number	61788-46-3	68155-27-1
Registration Number (Clariant)[1]		
Chemical Name	Amines, hydrogenated tallow alkyl	C16-18-(even numbered) -alkylamines
EC Number	262-976-6	292-550-5
CAS Number	61788-45-2	90640-32-7
Registration Number (Clariant)[1]		
Chemical Name	Amines, tallow alkyl	C16-18-(even numbered, C18-unsaturated)-alkylamines
EC Number	263-125-1	268-219-6
CAS Number	61790-33-8	68037-95-6
Registration Number (Clariant)[1]		
Chemical Name	(Z)-octadec-9-enylamine	C16-18-(even numbered, saturated and unsaturated)-alkylamines
EC Number	204-015-5	627-034-4
CAS Number	112-90-3	1213789-63-9
Registration Number (Clariant)[1]		
Chemical Name	Octadecylamine	Octadecylamine
EC Number	204-695-3	204-695-3
CAS Number	124-30-1	124-30-1
Registration Number (Clariant)[1]		

Comments on CLH-Report

Industry Executive Summary

APAG Consortium representing the manufacturers of Primary alkyl amines are concerned that the CLH Report provided by ECHA on October 19, 2010 does not take into account the additional information provided in the REACH Registration Dossier submitted in August 2010. The additional data in our REACH Registration Dossier are especially important in the area of Bioaccumulation which is updated and reflecting state of the art. This is especially important as this has a considerable influence on the Environmental Classifiction. Industry agrees on the R50/Acute class but disagrees with R50/Chronic Class

1. Primary alkyl amines are readily biodegradable and readily transformed in fish which results in a BCF < 500 L/kg wwt. Therefore it is not justified to assign any long-term effect under CLP. In the table below the new data is presented in an abbreviated form but additionally a comprehensive description of our new data and conlcusions are given in the files attached to these Industry comments. APAG wants to stress that the Environmental classification proposed in the CLH Report is not reflecting the state of knowledge and is therefore not acceptable.

With regard to "Human Health", APAG would like to emphasise that the classification & labelling proposals which were discussed and agreed at TCNES level and which were reported in the Transitional Dossier to ECHA and the European Commission are not in line with the respective proposals given in the CLH dossier. Since the

CLH report does not contain any new information compared to the Transitional Dossier and, moreover, does not take into account additional data / arguments provided in the REACH CSR, Industry cannot entirely agree with the extended classification & labelling proposals as stated in the CLH document.

General Comments

CLH-Dossier by MSCA	Comments to CLH-Dossier by Industry
Pg.1: (Z)-octadec-9-enylamine has already been prioritised under (EEC) No 793/93 in a substance group approach for 5 primary alkyl amines. This approach, risk assessment and classification and labelling have already been agreed within the Member States at a technical level (TCNES, TC C&L).	It should be noted that the classification and labelling regarding HH agreed at TCNES level (TCNES IV 08; I 07) included the following classification proposals: Xn: R22; R48/22; C: R34 which are not in line with the proposals given here.
pg. 7: Proposed classification based on Directive 67/548/EEC criteria: (Z)-octadec-9-enylamine has already been prioritised under ESR (Regulation No (EEC) 793/93). The group approach and risk assessment were also agreed at a technical level (TCNES). However, the risk evaluation work for this substance was not finalised by 1 June 2008, but reported in a transitional Dossier to ECHA and the European Commission. With regard to human health, the following classification/labelling is proposed: Xn,C; R 22-35-37-48/22	It should be noted that the group approach and risk assessment agreed at TCNES level included the following classification proposals: Xn: R22; R48/22; C: R34 which are not in line with the proposals given here. The proposals stated here therefore are not in line with the agreed classification at TCNES IV 07 and I 08 with regard to the R35 and R37. Moreover, the R35 is also in contradiction to the conclusion presented in table 5 on pg. 22 and to the conclusion on pg. 40 of the CLH document itself (here the R34 is concluded like in the transitional dossier). Industry does not disagree per se that "skin corrosivity" implies "respiratory irritancy" as well, however like for eye irritation a separate classification seems not be necessary. Nevertheless Industry does not oppose to include the classification with R37 for primary amines which are corrosive to skin, i.e. (Z)-octadec-9-enylamine .
pg. 7: Proposed classification based on GHS criteria: With regard to human health: Acute Tox 4, H302; Skin Corr 1B, H314; STOT SE 3, H335; STOT RE 2, H373 (Harmful if swallowed, causes severe skin burns and eye damage, may cause respiratory irritation, may cause damage to organs (gastro-intestinal tract, liver, immune system) through prolonged or repeated exposure)	Industry agrees with the proposed classification "Acute Tox 4, H302; Skin Corr 1B, H314; and STOR RE 2, H373 (Harmful if swallowed, causes severe skin burns and eye damage, may cause damage to organs (gastro-intestinal tract) through prolonged or repeated exposure). However, although it is indisputed that skin corrosive substances will also posess a concentration dependent respiratory irritating potential, a separate classification seems not to be indicated (comparable to eye irritation). With regard to H373 (STOT RE 2) Industry would like to point out, that the effects interpreted as "indications of immunosuppres-sion"are clear secondary effects due to the observed irritative changes and inflammatory events observed in the respective repeated dose toxicity study at higher doses tested.
pg. 8: Physico-chemical properties (table 1)	Industry has established a lot of new and important physico-chemical data which allow enhanced assessment. These new data are included in the REACH Registration Dossier of this substance which was submitted end of August 2010. For a matter of convenience these data have been compiled in a separate document to these Industry comments provided to ECHA.
pg. 22: Table 5: Overview of the primary alkyl amines/amine	Primary amines are not considered to be mixtures, but substances of natural origin with a variable composition (UVCB, C-chain-

Pg8: DE: Thank you for the information.

Pg22: DE: Thank you for the

			mixtures included in this CLH report *	length wise).	information. Your comment was taken into account. Pg23: DE: Thank you for the comment. DE: Thank you for the information. The given values for the water solubilities of different alkyl	
			pg. 23: mixtures	Primary amines are not considered to be mixtures, but substances of natural origin with a variable composition (UVCB, C-chain-length wise).		
			pg. 23: The presence of one or more double bonds might account for additional chemical reactivity – and, thus, different biological activity - in unsaturated vs. saturated fatty primary amines.	Although Industry agrees that the presence of double bonds may influence chemical reactivity, the same conclusion with regard to biological activity is speculative and without any scientific proof. In addition, it is unclear how this may relate to justify the proposed classification & labelling.		
			pg. 23: For this reason, at most slight differences, if any, in nucleophilic double bond reactivity, which in addition might as well be balanced by enhanced steric hindrance in the longer-chain amines, are expected between n-tetradec-9-enylamine, the major unsaturated constituent of the coco alkyl amines, n-hexadec-9-enylamine (strong in tallow and hydrogenated amines), or n-octadec-9-enylamine (tallow amines, (Z)- octadec-9-enylamine).	Hexadec-9-enylamine is one constituent of tallowalkylamines, however, in hydrogenated tallow amines, by definition, major parts of the double bonds have been converted to saturated bonds by hydrogenation with H2 in presence of a catalyst and thus, we would also like to point out, that unsaturation is not „strong“ in hydrogenated amines but quite the opposite. In any case it is unclear how this relates to Oleylamine.		
			pg. 23: Chapter of „Saturated vs. unsaturated primary amines“	Industry disagrees with the mechanistic considerations given in this chapter. Additionally, it is unclear how this relates to classification & labelling. Industry proposes to only refer to the common biological principles regarding metabolisation of fatty amines and/or fatty acids via desamination and subsequent β-oxidation.		
			pg. 24: Apart from the calculated water solubility of 0.12 mg/L for tallow alkyl amines, all other alkyl amines are insoluble in water. Log POW has been calculated for all amines with the exception of coco alkyl amines and ranges from 7.1 to 7.71.	Please note that due to the Reach registration process new data has become available (see see attachments No. 2 and 3). In addition, Industry cannot entirely agree to the conclusion that all other amines are considered to be insoluble based on the water-solubility of tallow alkyl amines. For shorter alkyl-chains, like present in higher amounts in cocoalkylamines compared to tallow, the influence of the hydrophilic amine-group (NH2) on the total molecule is increased while the hydrophobic character - due to the unpolar alkylchains – is reduced. Subsequently the watersolubility is expected to increase. This is verified by the newly generated data presented in the Reach- Dossiers and in the attachments No. 2 and 3.		
			pg. 85: Additionally, remarkable work has been done to gather and evaluate information. The effort already done to propose harmonised C&L even for issues other than CMR and RS should not be dismissed in order to avoid wasting of resources. Moreover, it is pointed out that a grouping approach is followed in the current CLH report. Each registrant for any of the substances in this report will most likely only have access to a limited subset of the data presented here. In such a scenario, contradictory entries in the inventory (which would THEN trigger	Industry agrees that enormous efforts have been undertaken with regard to the evaluation and assessment of primary alkyl amines. Industry therefore supports the intention to not dismiss the work already performed. However, compared to the existing EU-Risk-Assessment Dossier it should also be noted that new data due to the requirements of REACH has been generated additionally, which has not been considered fully or partly by the MSCA during preparation of this CLH-Dossier. Since it is a legal requirement to share all data available in the SIEF/consortia, the argument that registrants will have only access to a limited subset of the data presented in the CLH-Dossier is incomprehensible to understand and not true. In the opposite, the data basis for the CLH-Dossier		

		the need for CLH) can be expected with high probability. The current CLH proposal therefore constitutes an efficient way of assuring a high quality standard by proactively evading conflicting C & L and - as a consequence - avoiding time-consuming follow-up work.	have been published already in the Transitional Dossiers by the same MSCA early 2010 and thus prior to the REACH-CSR prepared by Industry. Taking into account that Industry is obliged to register these amines before the first deadline 2010, it is not understandable publishing a CLH-Dossier without taking into account the Reach-Dossier already submitted in August 2010. This action by the MSCA after the registration of all primary fatty amines is quite the opposite of "an efficient way of assuring high quality and … avoiding timeconsuming follow-up work".	amines (pg. 21 ff of this document) will be taken into account.	

Carcinogenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	We agree with the proposal.	DE: Thank you.	No additional comments

Mutagenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	We agree with the proposal.	DE: Thank you.	No additional comments

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	We agree with the proposal.	DE: Thank you.	No additional comments

Respiratory sensitisation

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	We agree with the proposal.	DE: Thank you.	No additional comments

Other hazards and endpoints – Acute Toxicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	Acute toxicity: For coco alkyl, the LD50 value of 2040 mg/kg/day (Hazleton laboratories Europe Ltd, 1979a) does not appear to be correct given the number of animals reported to have died at each dose level. If the LD50 is in fact higher, does this affect the overall conclusion on classification for this substance?	DE: As indicated in the report, we did not have access to the study report itself, but only to an RSS by Toxicology Regulatory Services Inc. on behalf of US EPA. Admittedly, the uncertainty in the LD50 value is quite high,	We agree with DE

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
			cf. also the confidence band given. However, the question whether a higher LD50 value should have been identified in this study is not relevant for the classification proposal for coco alkyl amines. The relevant study here is the one by Sterner & Chibanguza, (IBR Forschungs GmbH 1983a) yielding an LD_{50} of 1300 mg/kg bw/d.	

Other hazards and endpoints – Irritation corrosion

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	Skin irritation	DE: Because of the limited	For skin irritation we

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		For hydrogenated tallow alkyl and octadecylamine, many of the skin irritation studies were conducted on three animals. According to the DSD and CLP, for studies with 3 animals, the averages should be calculated per animal. Would it be possible to present the findings in this way to make it easier for the reader to compare the results with the criteria? The cut-off values for skin irritation differ between the DSD and CLP. It is not clear whether these differences have been taken into account in your proposal for classification as a skin irritant. Respiratory irritation It would be useful to provide more details of the specific effects you consider justify classification with R37. In the inhalation study you state that irritation of the airways was observed; however, apart from nasal discharge, we could find no evidence of any effects on the upper respiratory tract in the study summary. As a proposal has been made to classify several of these substances as corrosive, classification with R37 may be superfluous, as respiratory irritation is implicit (although classification with EV071 should be considered). For those substances classified as irritant, we are currently not convinced that the justification for classification with R37 is sufficiently robust.	space in the 'Response' column we have addressed this comment in an appendix to this RCOM (Appendix 1).	support the DE opinion, while for respiratory irritation see the comments in the appendix 3. EUH071 seems to be not appropriate according to item 3.2.4.2 of the guidance on the application of the CLP criteria .

Date	Country/ Person/ Organisation/ MSCA	Comment		Response	Rapporteur's comment
02/12/2010	Germany / APAG Primary Fatty Amine Consortium / Industry or trade association	**pg. 40:** The author concluded that the test substance should be considered corrosive; the obtained results call for classification/labelling with C;R34 ('causes burns'; Centre International Toxicologie, 1999b). Consequently, the study authors concluded on classification/labelling with C;R34 ('causes burns'; Research and Consulting Company Ltd., 1994b).	Industry fully agrees with the conclusion drawn by the authors of the respective studies. However we noted (see your table 5 on pg. 22) that "Oleylamine" is classified with R35 as per your proposal in the CLH document. However, this is not in line with the proposal given in the transitional risk assessment dossier where an R34 was indicated. This should be corrected.	DE: Because of the limited space in the 'Response' column the extensive comments by APAG are addressed in an appendix to this RCOM table (Appendix 2).	See our comments in the Appendix 3
		pg. 42: For the following reasons it is therefore proposed to classify/label all of the amine mixtures covered by this report for respiratory irritation	Industry agrees to consider that skin corrosive primary fatty amines will have potential respiratory irritative effects. However, Industry disagrees that all of the amine „mixtures" should be classified for respiratory irritation. On the one hand, primary fatty amines are not representing "mixtures" but according to the REACH definition "substances". On the other hand, the reasons given are not backed up by the definition of STOT SE criteria as given in chapter 3.8 of the CLP-regulation (EC 1272/2008). Industry also disagrees with the general statement about an interrelation between cationic surfactants and respiratory irritation. Although industry agree that primary alkylamines classified as corrosive may also possess a certain respiratory irritation potential, this cannot be generally translated to primary alkylamines considered to be skin irritants. In this respect industry disagree that "skin irritation" without any additional indication is triggering classification as respiratory irritant. This view is in line with a lot of substances displaying skin but not eye irritating properties. Based hereupon, industry disagrees with the proposed classification of hydrogenated tallow alkylamine and octadecylamine with R37 and/or STOT SE 3, H335 respectively.		
		pg. 43: 5.3.4.1 Skin irritation From the available animal tests, it is concluded that the three primary amine mixtures containing significant amounts of unsaturated amines have to be classified/labelled as corrosive (coco alkyl. tallow alkyl: C;R35/Skin Corr 1A; H314, (Z)-octadec-9-enylamine; C;R34/Skin Corr 1B), while for the other two amines (hydrogenated tallow and octadecylamine), classification/labelling as Xi;R38/Skin Irrit. 2; H315 is warranted. Again, it is left to speculation whether the difference in bioactivity of the 'saturated' vs. 'unsaturated' amines can be explained in terms of an altered bioavailability, by direct reactivity of the double bond(s), or by metabolic toxification (cf. introduction to this chapter and section 5.1).	Industry agrees with the conclusions drawn that coco alkyl amine, tallow alkyl amine and (Z)-octadec-9-enylamine have to be classified as corrosive to skin. However, Industry disagrees with the direct and very general translation of risk phrase R35 - causes severe burns into "skin corrosivity category 1A" and R34 - causes burns into "skin corrosivity category 1B". Based on the definitions given in the CLPregulation (EC 1272/2008), skin corrosivity category 1A relates to substances where the corrosive effect occurs after an exposure period of </= 3 minutes within an observation period of </= 1 hour, whereas category 1B relates to an exposure period > 3 minutes </= 1 hour and the occurrence of the corrosive effect within an observation period of </= 14 days. All primary alkyl amines under discussion have been investigated using an exposure period of 3 minutes, but in all cases the corrosive effect was only visible considerably later		

Date	Country/ Person/ Organisation/ MSCA	Comment		Response	Rapporteur's comment
			than 1 hour. Since the exposure time is very close to the cut-off of 3 minutes but the occurrence of the corrosive effect clearly exceeds the cut-off of 1 hour for the observation period (in most cases effects have been observed within 7 to 14 days), a classification of above mentioned primary alkyl amines as skin corrosive category 1B is more plausible and scientifically appropriate.		
		pg. 43: 5.3.4.3 Respiratory irritation In contrast to eye irritation, C & L for respiratory irritation is not implicit with C & L for corrosivity both under Dir. 67/548/EEC and Reg. (EC) No. 1272/2008. No human data and no specific animal tests for respiratory irritation of the primary amine mixtures are available. However, based on general knowledge as well as on a synopsis of data from acute and repeat-dose studies it is proposed to classify/label all of the amine mixtures covered by this report for respiratory irritation, i. e. as/with Xi;R37 ('irritating to respiratory system') or STOT SE 3;H335 ('may cause respiratory irritation'), respectively.	Industry agrees that there are no specific animal tests available to evaluate respiratory irritation. Industry also agrees that it is indisputable that skin corrosive materials may also possess a respiratory irritative potential. However, Industry disagrees with the general statement to classify/label all of the amine „mixtures". Despite the fact that primary alkyl amines should not be considered "mixtures" but "substances", Industry wonders about the basis "based on general knowledge" as rational for this classification proposal. However, since Oleylamine should be classified as skin corrosive category 1B Industry agrees to also classify with R37 and STOT SE 3 H335 respectively, although Industry is of the opinion that the classification as skin corrosive implies that classification as respiratory irritant is included (comparable to eye irriation). Although industry agree that primary alkylamines classified as corrosive may also possess a certain respiratory irritation potential, this can not be generally translated to primary alkylamines considered to be skin irritants. In this respect industry disagree that "skin irritation" without any additional indication is triggering classification as respiratory irritant.. This view is in line with a lot of substances displaying skin but not eye irritating properties. Based hereupon, industry disagrees with the proposed classification of hydrogenated tallow alkylamine and octadecylamine with R37 and/or STOT SE 3, H335 respectively.		

Other hazards and endpoints – Skin sensitisation

Date	Country/ Person/ Organisation/ MSCA	Comment		Response	Rapporteur's comment
02/12/2010	Germany / APAG Primary Fatty Amine Consortium / Industry or trade association	**pg. 44:** 5.5.1.2 Animal data Amines, coco alkyl In summary, due to methodological deficiencies of this study, it does not allow for a clear decision on the potential of primary alkyl amine mixtures to cause skin sensitisation.	Industry disagrees with this statement. The study on Cocoalkylamine is in full compliance to the respective EU- and OECD test-guidelines. Moreover, the test strategy was carefully adapted according to the results obtained in each of the experimental phases (screening test, main test) in order to ensure best possible animal welfare. With regard to the interpretation of	DE: Because of the limited space in the 'Response'	See our comments in the Appendix 3

Date	Country/ Person/ Organisation/ MSCA	Comment		Response	Rapporteur's comment
			the results, it is clear scientific and regulatory practice, that a 20% incidence without any additional indications should not be regarded a borderline result. Thus it is concluded that Cocoalkylamine represents no significant skin sensitisation hazard.	column the extensive comments by APAG are addressed in an appendix to this RCOM table (Appendix 2).	
		pg. 45: Amines, hydrogenated tallow alkyl Since the test substance is nearly insoluble in water, it appears doubtful that reported nominal test concentrations of up to 10 % could have been achieved. In consequence, these study results are not valid and cannot be used as a basis for classification/labelling.	The study was conducted according to accepted scientific standards and the report is well referenced and documented. Based on existing guidelines, also solids can be tested for skin sensitisation when incorporated in appropriate vehicles. Thus, insolubility in water is not a criterion to exclude a material from testing. It is guideline conform to use in such situations suspensions in appropriate vehicles (e.g. water). Therefore, challenging whether a 10% solution/suspension in water was achieved or not is thus no reason on its own to conclude that the results are not valid. Considering all available information Industry agrees with the conclusion of the study director that hydrogenated tallow alkylamines do not represent a significant skin sensitisation hazard.		
		pg. 45: 5.5.3 Summary and discussion of sensitisation The available experimental data for coco and hydrogenated tallow alkyl amines are either inconclusive or of insufficient validity, and thus do not allow for a conclusion on the skin sensitisation potential of the alkyl amines assessed in this dossier. At least for coco alkyl amines, skin reactions have been observed at a level slightly below, but borderline to the classification threshold, but an insufficient number of animals has been used in the respective test. In summary, no data on respiratory sensitisation are available, while the database is inconclusive with respect to skin sensitisation. It is noted, that if new data were to be generated, the test substance should be one of the mixtures containing a significant amount of unsaturated fatty alkyl amines, as these compounds might show higher reactivity than their saturated analogues. It could then be considered justified to read-across the results to those mixtures exclusively or predominantly containing unsaturated fatty alkyl amines.	Industry disagrees with this statement, especially that read-across cannot be applied to all members of the group of primary fatty amines. For 2 primary fatty amines experimental data is available and was discussed very extensively at TCNES level, great care was undertaken by Industry to avoid unnecessary extensions of test protocols due to animal welfare reasons. Both available studies do not reveal major concerns with regard to a significant sensitization potential. Additionally, from all available experience with primary fatty amines no indications of such a risk is identifiable. Industry has great reservations in testing corrosive / strong skin irritative materials for skin sensitization due to animal welfare reasons. This view is also expressed in various official statements, test guidelines and regulatory directives (e.g. REACH regulation 1907/2006, Annex VII, point 8.3, column 2).		

Other hazards and endpoints – Repeated dose toxicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	Repeat dose toxicity In the summary for repeat toxicity, more consideration is needed to determine whether some of the severe health effects observed (death, anorexia and erosion of the gastrointestinal mucosa) are a reflection of true repeated exposure or, in fact, due to the corrosive nature of the substances (i.e. an acute effect). Of the other effects observed at non-irritating doses, none of them would appear to be sufficiently serious in nature to warrant classification. In addition, we would also consider it beneficial if table 7 was expanded to include information on the key effects and the dose levels at which they were observed.	DE: We believe that the reasoning behind the proposal for classification has been made sufficiently clear under section 5.6.5. As presented there, the proposal is based on relevant effects such as delayed mortality and functional disturbances due to accumulation of test material in specific organs. Many of these effects were observed at non-irritant dose levels.	We agree with DE opinion: the observed effects even at non-irritant dose level support a classification R48/22- STOT RE2 H373 for all amines

Other hazards and endpoints – Aspiration hazard

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment

Date	Country/ Person/ Organisation/ MSCA	Comment		Response	Rapporteur's comment
02/12/2010	Germany / APAG Primary Fatty Amine Consortium / Industry or trade association	**pg.31:** Normally, aside from concrete evidence in humans, classification/labelling of a substance for aspiration hazard is triggered if it is a hydrocarbon with a kinematic viscosity < 7 x 10-6 m2/s at 40 °C. The latter can be obtained as the quotient of dynamic viscosity (,in Ns/m2 or Pas) and density (in kg/m3). The following arguments pro/contra C & L for aspiration hazard have been identified: Table 6: Viscosity of alkyl amine mixtures (Source: MSDS) As a general trend, it can be seen that kinematic viscosities are below or borderline to the critical value of 7 x 10-6 m2/s.	Please note that due to the Reach registration process new data has become available which allowed a more reliable calculation of the kinematic viscosity based on the measured dynamic viscosity (see attachments No. 2 and 3). Example: Viscosity of Octadecylamine, which is the substance with the highest viscosity determined and thus can serve as a worst case. Dynamic viscosity has been determined 4.17mPa*s which converts to 0.00417 Ns/m2 [1] based on a density of 700 to 900 kg/m3 this results in a calculated dynamic viscosity of: 0.00417 Ns/m2 : 900 kg/m3 = 4.63x10-6 m2/s. This result is by factor 1.5 below the critical value of 7x10-6 m2/s Thus, kinematic viscosities are not considered to be borderline, but well below the critical value.	DE: Because of the limited space in the 'Response' column the extensive comments by APAG are addressed in an appendix to this RCOM table (Appendix 2).	See our comments in the Appendix 3.
		pg. 32: On the other hand, severe lung damage was frequently observed following repeated oral administration of primary alkyl amines to rats, both by gavage and in the diet. However, in none of the cases it was possible to attribute these findings with sufficient certainty to substance treatment and to rule out other, (micro)biological causes (cf. section 5.6).	Lung effects after repeated oral administration via gavage is a frequently observed phenomenon observed with a lot of different compounds not restricted to primary alkylamines. However, industry disagree with the statement that "severe lung damage" was frequently observed with primary alkylamines following repeated oral administration both via gavage and the diet. The rapporteur himself states in the EU risk assessment on primary alkylamines that these findings are not reflecting direct systemic toxic effects but indirect local effects due to secondary inhalation of foamy particles instilled originally into the stomach (reflux-phenomenon).		
		pg. 32: Nevertheless, even considering that observations such as breathing impairment and corresponding lung noises or histopathological signs of acute or chronified pneumonia potentially can be traced back to a great variety of factors, it is quite striking, how many acute and repeatdose study reports cited in the present report make reference to such symptoms following administration of primary alkyl amines. Conclusion For the primary alkyl amines addressed in this report, the database with respect to aspiration hazard is inconclusive and thus insufficient to demand corresponding classification/labelling.	The reason for this statement is incomprehensible. It is neither conspicuous nor striking that some materials quite often display this phenomenon when repeatedly administered orally via gavage. Even in the existing risk assessment the rapporteur is accepting that the observed effects in studies with repeated gavage administration of test compounds are not reflecting direct systemic toxic effects but indirect local effects due to secondary inhalation of foamy particles instilled originally into the stomach (reflux-phenomenon).		
		pg. 33 5.2.5.4 Aspiration There is some evidence, that primary alkyl amines might pose an aspiration hazard and classification/labelling	It is not quite clear to Industry where the indicated part of "evidence" is coming from. However, based upon the new data with regard to the kinemetic viscosities		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		with R65/H304 might be warranted, but overall the available data are insufficient to arrive at a conclusion with sufficient certainty. (see our comments), Industry proposes to remove this entry from the CLH-Dossier.		

Other hazards and endpoints - Environment

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/11/2010	United Kingdom / Member State	Environmental sections We appreciate these substances are difficult to test however we have some concerns about how the bioaccumulation study was interpreted (section 4.3.1.2). We do not think the nominal water concentration should be used to provide "Cwater". If possible we think the measured concentrations should be used to represent the aquatic exposure, particularly as we know the dissolved concentrations have declined significantly during the study. We think it is important the values used reflect what the organisms were actually exposed to. We also do not think that the whole fish body burden should be used to represent the uptake by fish. Bioaccumulation represents the cross-gill uptake, therefore we suggest the results after skin/mucus removal and solvent washing should be used to represent the fish uptake concentration. It is important that we exclude substance adsorbed to the exterior of the fish from the BCF calculation. We appreciate a non-standard protocol was used, however if available, a measurement of lipid concentrations would be useful to allow derivation of a lipid BCF. We also think the study summary in the dossier should indicate whether the study was flow-through or semi-static. We think the long-term invertebrate data should be included in the dossier (section 7.1.1.2). These data were used for the aquatic PNEC in the previous ESR assessment, and will be needed to allow chronic classification once the 2nd ATP is in force. We are unsure if new long-term data are now available, however the previous data appear to suggest a different chronic classification may apply, and we think this should be considered now. The data may also help provide a weight of evidence at this stage (i.e. prior to the 2nd ATP) where we are applying a surrogate chronic classification based on acute ecotoxicity data and difficult-to-interpret bioaccumulation data. On a minor editorial point, for clarity we think the specific acute aquatic value used for classification and the M factors should be discussed in section 7.6."	Thank you for this comment. We adopted the evaluation of the bioaccumulation study according to UKs comments. We included the mean recovery rate of the test substance in the calculation of the exposure concentration. Unfortunately, no lipid content of the test fish was provided in the study summary. We agree that in the BCF may be calculated considering the amount taken up by fish. When recalculating the BCF using the mean exposure concentration and the mean concentration in fish after each of the two washing treatments the BCF ranged from 385 to 225. However, we only agree to a certain extent, because the strong sorption propensity of the test	We agree with the approach of using body burden conc and estimated real water concs. as the most favourable interpretation of the BCF test. We do no see justification in removing the mucus/scales, previously to washing fish with methanol and chloroform.

Date	Country/ Person/ Organisation/ MSCA	Comment		Response	Rapporteur's comment
				amine to fish´s surface should not be completely disregarded. It could be argued that the substance adsorbed in the mucus layer may diffuse into the fish and thus may become potentially bioaccumulative. If the BCF is based on whole body burden concentrations, it might reach 1150. Concerning the long-term toxicity data we included recalculated 21-d $NOEC_{repro}$ values for daphnia, provided by industry as attached document in RCOM.	
02/12/2010	Germany / APAG Primary Fatty Amine Consortium / Industry or trade association	**pg. 16:** Based on the results of all tests primary long-chain alkyl amines can be classified as "readily degradable, but failing the 10 d window".	Primary alkyl amines are readily biodegradable, the 10d window criteria is not meaningful for surfactants as under environmental conditions e.g. pH 7 99.98% of the amine is protonated to the corresponding cationic surfactants (see Detergents Directive 2004/648/EC and additional sources: 1) Cefic Paper: The Relevance of the 10d Window in the Context of the Assessment of ready Biodegradability for Surfactants (March 2008) 2) OPPTS 835.3140. 3) Richterich, K. and J. Steber (2001). The time-window an inadequate criterion for the ready biodegradability assessment of technical surfactants. Chemosphere 44, 1649-1654.	There is a difference between "readily biodegradable" and "readily biodegradable but failing 10-days-window". The latter corresponds to the assessment as rapidly biodegradable as laid down in the detergent regulation. The term readily biodegradable is clearly defined and includes both reaching pass level and fulfilling the 10-days-window. It is important to keep the quality of the conclusion readily biodegradable	We agree
		pg.18: For octadecylamine no experimentally determined log KOW has been stated, but Clariant (2001) reported a calculated log KOW of 7.7. Under environmental conditions a part of the primary amine proportion might be protonated yielding alkyl ammonium ions. Accounting for the protonation equilibrium of primary alkyl amines in environmental media the log KOW might be adjusted to a lower level than 7, but an exact quantification is not possible.	Primary alkyl amines are a strong bases with a pKa of 10.6. Under environmental conditions (pH 4-9) more than 99% of the free amine is protonated to the cationic ammonium salt which is a surfactant. These facts are reported in detail in the REACH Registration Dossier submitted end of August 2010.This means not only the octanol water partitioning behaviour of the free amine (log Kow 7.4 estimated with US KOWWIN) but also the measured Log Coct/Cwater of the protonated Primary alkyl amines of $\leq$ 3.9 has to be taken into account.		Agreed

Date	Country/ Person/ Organisation/ MSCA	Comment		Response	Rapporteur's comment
		pg. 18 Measured bioaccumulation data	APAG has tried to carry out a Bioaccumulation study following the OECD305 protocol. This attempt has failed as major validity criteria could not be met because of the inherent properties of the test substance 1-Hexadecanamine (HDA) which was chosen as model compound. HDA is almost completely protonated under test conditions, sorbs strongly to the glass wall of the aquarium and makes a constant water concentration under flow through conditions impossible. Another major impact is that the cationic sorbs to the negatively charged mucous of the fish's surface. Under environmental conditions sufficient DOC and suspended matter in the river would prevent major substance accumulation on the fish. These are only the most important issues which has made the study a failure. Therefore Industry wants to stress that taking any data from this invalid study to estimate a BCF cannot be accepted. In the meanwhile more reliable data are available and also different approaches to obtain BCF from amine containing surfactants have been followed. Industry has setup a Weight of Evidence Approach and has derived a BCF of 173 L/kg wwt for Primary alkyl amines. The approach uses a state of the art ADME model (Arnot and Gobas, 2003) with fully measured parameters including the (worst case) fish metabolic rate of 1-Hexadecanamine measued in an in-vitro test.The Weight of Evidence Approach with all available supporting data have been described already in the REACH Registration Dossiers for the above mentioned Primary alkyl amines but is also attached as detailed document to Industry comments of the CLH Dossier (see attachments No. 2 and 3).	consistent throughout all chemicals. Either conditions are met or they are not and this is independent from the reasons. Though it is important to know the reasons for not fulfilling 10-d-w in the pattern of persistency assessment it nevertheless is not valid to ignore the 2nd condition for an assessment as readily biodegradable. Besides, a substance assessment as readily biodegradable but failing 10-days-window already exonerates the P criterion. We agree with this statement and used the provided log K_{OW} for the amine hydrochlorides to give a realistic log K_{OW}-range for tallow alkyl amine. We agree that this study does not comply with certain requirements concerning validity. However, as no new experimental data were generated during the	We agree. Also 50% substance recovery from wter should be accounted. The BCF study also considers the metabolic degradation in fish as a living organism.
		pg. 19: The derivation of one realistic worst case BCF for the 5 assessed primary alkyl amines based on the indicative bioaccumulation test using hexadecylamine is possible by respecting all physico-chemical properties influencing bioaccumulation (Table 4).	The approach taken in the CLH Dossier is not adequate for cationic surfactants. Instead a Weight of Evidence Approach is currently the most reliable scientific way to derive the BCF of this cationic surfactant Oleylamine hydrochloride (see details above)		
		pg. 20: Summarising all, a similar bioaccumulation potential can be hypothesised for these 5 long chain alkyl amines with minor differences in rate of metabolism. Because all 5 fatty amines are considered as "readily biodegradable" these differences in metabolism can be disregarded and it is appropriate to assume the same realistic worst case BCF of 1200 as determined for hexadecylamine.	The approach to use data of the invalid Bioaccumulation study is not acceptable for Industry. Instead a Weight of Evidence Approach which takes into account metabolic degradation in fish supports a BCF of 173 L/kg wwt for all 5 n-Primary alkyl amines.		
		pg. 20:	Physico-chemical data like log Kow alone cannot address the BCF		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Table 4: Comparison of physico-chemical properties influencing bioaccumulation / of a substance which is readily biodegradable as well as it is metabolised in fish. Comparing the octanol water partitioning data for the free amine and the protonated amine it appears that the partitioning coefficient of the the protonated amine is more than 3 orders of magnitude lower compared to the partitioning coefficient of the unprotonated free amine. Thus, it can be assumed that uptake of the protonated form is reduced **pg 20:** BCF (no experimental data available) 200-2400, 1200 as realistic worst case / As said before using data to derive the BCF for Primary alkyl amines from an invalid bioaccumulation study cannot be accepted by Industry. Instead the Weight of Evidence Approach described before is most adequate. **pg.21:** As the adsorbability of long-chain amines is very high and desorption rate is expected to be low, the rapporteur strongly advocates an incorporation of surface loading in determination of body burden respectively BCF. Thus, all available informations indicate for a high bioaccumulation potential, probably with BCF > 1000. Using the results of the indicative bioaccumulation study, the rapporteur proposes to use a realistic worst case BCF of 1200 (whole fish burden and nominal amine concentration) for C&L purposes. This fact is further supported by the high log KOW of about 7. / As said before the test setting described by OECD 305 guideline cannot address the test issues related to the inherent properties of the cationics reliably. Under realistic environmental conditions with DOC, suspended matter and substance concentrations of around 0.1 µg/L coating of the fish's surface as observed under OECD 305 test conditions will not occur. And again: any derivation of a BCF from the invalid OECD 305 study is not acceptable for Industry. Using solely the log Kow only to assess the BCF for a substance which is biotransformed is inadequate. **APAG POSITION ON THE ENVIRONMENTAL CLASSIFICATION OF n-PRIMARY ALKYL AMINES (C12 TO C18)** 0. Executive Summary *Ecotoxicity* n-Primary alkyl amines (C12 to C18) are ecotoxic. Algae and Daphnia are the most sensitive species in acute river water tests but the effects are in the same order of magnitude. The following results are corrected by a worst case factor of 10 to address the mitigating effect on ecotoxicity in river water due to sorption to DOC and suspended matter (APAG 2010). The ErC 50 (72h, corr.) for algae is in the range of 0.01 and 0.05 mg/L and the EC50 (48h, corr.) for Daphnia is in the range of 0.02 and 0.1 mg/L. As the corrected EC50 values are < 1 mg/L and with respect to ecotoxicity a N, R50, M factor 10 for mixtures has to be assigned under DSD 67/548/EEC and Acute (short-term) aquatic hazard H400, M factor 10 for mixtures. The M factor of 10 has to be assigned as the lowest EC50 is < 0.1 mg/L but >= 0.01 mg/L. *Ready biodegradability* The n-Primary alkyl amines (C12 to C18) are ready biodegradable. The criteria of the 10 d window is not fulfilled but also not required for surfactants (see Detergents Regulation 2004/648/EEC, CEFIC 2008, Richterich et al. 2001, US EPA 2008a). Based on the biodegradation property a long-term effect on the aquatic environment is not expected. *Bioaccumulation* Due to the inherent properties of these substances (cationic surfactants under environmental conditions) currently no Guideline for a Fish Bioaccumulation study exists which could overcome the test issues. Instead a Critical Body Burden Approach based	preparation of REACH-dossiers, we think this study is still capable to provide an estimate for the bioaccumulation behavior. We re-evaluated the study using the mean recovery rate of the amine in the exposure solution and the mean concentrations in fish after the two washing treatments. Assuming that the BCFs might range from 225 to 385 for fish, rinsed with methanol/acidified methanol, which are in the same range of BCF as derived by APAG. However, the strong sorption propensity of the test amine to fish´s surface should not be disregarded. In particular the substance adsorbed in the mucus layer might diffuse into the fish and thus might become potentially bioaccumulative. If the BCF is calculated on whole body burden concentrations, it may reach 1150.	We agree that some of the BCF study results are difficult to interpret. C&L does not try to reflect what would happen in the environment, but display potential intrinsic properties. At this moment we are not sure how much appropriated is the use of environmental samples, specially in short-term tests. Even with the mitigation factor. Bioabalilability of the substance seems to be highly reduced. See Table 3 and lag periods of even c.a. 3 days, depending on the water, attributed to a high sorption tendency. Reg 2004/648 establises a control

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		on 21d Daphnia river water tests as well as a modelling approach covering Adsorption, Distribution, Metabolism and Excretion in fish with measured metabolic rates for 1-Hexadecanamine in vitro was carried out. In a Weight of Evidence Approach a BCF of 173 L/kg wwt. was chosen as the most adequate BCF determined to date of n-Primary alkyl amines (C12 to C18). Based on this BCF chosen a biococentration potential can be neglected from a scientific point of view. This view is supported by the B criteria for the PBT & vPvB Assessment of >2000 and >5000. Due to the stringent BCF criteria of the DSD a R53 has to be assigned formally. The less stringent BCF criteria of CLP do not lead to a chronic classification. To avoid that the classification under DSD is in conflict to the classification under CLP it is proposed to skip the R53 which is justified from a scientific point of view. ***Proposal for a Harmonized Environmental Classification*** **Dangerous Substance Directive 67/548/EEC** N, R50 R53 is not assigned to avoid a conflict with the CLP classifcation (see explanation above) M factor 10 for mixtures **Classification, Labelling, Packaging Regulation 2008/272/EC** Acute (short-term) aquatic hazard, H400, M factor 10 for mixtures **1. Background information** *Risk Assessment under Existing Substance Regulation 93/793/EEC* An EU Risk Assessment Group Approach for five n-Primary alkyl amines was carried out recently but only the Environmental part was accepted by Authorities and Industry. This has included a proposal for an Environmental classification N, R50/53. *Registration Dossier under REACH Regulation 1907/2006/EC* A Group Approach for the five n-Primary alkyl amines which were already assessed under the Existing Substances Regulation 93/793/EEC was carried out and registered under REACH. Additionally 1-Dodecanamine which was not part of the Group approach with the five n-Primary alkyl amines was added to the Group approach and registered under REACH as a Group approach with six n-Primary alkyl amines. **2. Substances covered** The substances covered in this Position paper on the Environmental Classification of n-Primary alkyl amines are given in the Table 2.1 below. The table contains the REACH name of the substance, EC and CAS No. as well as a Public name which corresponds to the naming of the five n-Primary alkyl amines of the EU Environmental Risk Assessment under ESR 93/793/EEC.	Please refer to the comment above. Based on the similarity of most of the physico-chemical properties of the assessed fatty amines, a read across BCF can be proposed for all 5 fatty amines. Considering only the fraction taken up into the fish tissue, the BCFs for hexadecanamine might be calculated for 225 and 385. This BCF-range may also be assumed for the 5 fatty amines discussed in this dossier. However, if the surface- adsorbed fraction of hexadecanamine is also considered as potentially bioaccumulative, a worst case estimate BCF of 1150 can be attributed to all 5 fatty amines in a similar manner by read-across.	procedures for detergents on the market: in the case of the cationic ones, an small activated sludge is applied (c.a. inherent degradation test). This is not the point for C&L.

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Table 2.1 n-Primary alkyl amines covered in this Pos. paper on Env.Classification **5 n-Primary alkyl amines covered by ESR 93/793/EEC and REACH 2006/1907** **Substance Name:** C16-18-(even numbered, C18-unsaturated)-alkylamines **EC Number:** 268-219-6 **CAS Number:** 68037-95-6 *Public name(s):* *AMINES, TALLOW ALKYL or Tallow alkyl amines (TA)* *EC Number:* *263-125-1* *CAS Number:* *61790-33-8* **Substance Name:** C16-18-(even numbered, unsaturated & saturated)-alkylamines **EC Number:** **CAS Number:** 1213789-63-9 *Public name(s):* *(Z)-OCTADECYL-9-ENYLAMINE* *EC Number:* *204-015-5* *CAS Number:* *112-90-3* **Substance Name:** Octadecan-1-amine **EC Number:** 204-695-3 **CAS Number:** 124-30-1 *Public name(s):* *OCTADECYLAMINE* *EC Number:* *204-695-3* *CAS Number:* *124-30-1* **Substance Name:** C16-18-(even numbered)-alkylamines **EC Number:** 292-550-5 **CAS Number:** 90640-32-7 *Public name(s):* *AMINES, HYDROGENATED TALLOW ALKYL or Hydrogenated tallow alkyl amines (HT)* *EC Number:* *262-976-6* *CAS Number:* *61788-45-2*		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Substance Name: C12-18-(even numbered)-alkylamines **EC Number:** 268-953-7 **CAS Number:** 68155-27-1 *Public name(s):* *AMINES, COCO ALKYL AMINES or Coco alkyl amines* *EC Number:* *262-977-1* *CAS Number:* *61788-45-2* **Registrant** LEAD: Clariant Produkte (Deutschland) GmbH **Additional n-Primary alkyl amine in Group Approach with the 5 amines (REACH)** **Substance Name:** Dodecan-1-amine **EC Number:** 204-690-6 **CAS Number:** 124-22-1 *Public name(s):* *Dodecylamine* *EC Number:* *204-690-6* *CAS Number:* *124-22-1* *Registrant* **LEAD: Clariant Produkte (Deutschland) GmbH** **Model compound for C12 to C18 n-Primary alkyl amines accepted by EU Authorities** **Substance Name:** Hexadecan-1-amine **EC Number:** 205-596-8 **CAS Number:** 143-27-1 *Public name(s):* *Hexadecylamine* *EC Number:* *205-596-8* *CAS Number:* *143-27-1* *Registrant* ***NOT REGISTRED UNDER REACH, no EU Risk Assessment under ESR*** **3. Substance properties to be addressed for the Env. Classification** **3.1 Ecotoxicity** Amines containing cationic surfactants are difficult to test in reconstituted water as they sorb strongly to glass walls and test organisms leading to highly variable results. Instead aquatic ecotoxicity tests carried out in river water deliver reproducible test results with limited uncertainty. As river water has a mitigating effect on ecotoxicity due to sorption of the amines to DOC and suspended matter a worst case mitigation factor of 10 should be applied to correct for the lower ecotoxicity observed (ECETOC 2003). Algae and Daphnia ecotoxcity data are in the same order of magnitude (Details see REACH Registration Dossiers of the n-Primary alkyl amines (C12 to C18). • **Characterisation of River water used in testing** The description of the Boehme water used for ecotoxicity tests of n-Primary alkyl amines (C12 to C18) is given below (extracted from a test report). The Böhme is a typical, highland river.		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Dilution water A natural occurring river water will be used as test media, cited *(Test medium)* hereafter as "Böhme". The dilution water will be frozenin 1- 50 L units. These units will be defrosted at least one day before water renewal. *Storage Conditions* Boehme water will be stored at –18 ± 2°C for a duration of at least 4 weeks until use. Freezing was found to be suitable to minimize the content of vital natural alga cells of the waters as well as to reduce microbial (bacterial) activity. A natural river water of agricultural background, middle reach of the river "Böhme", lower saxony was used as dilution water. **Table 3.1.1** Characterisation of the water of river Böhme River — **Boehme** Location — Dorfmark, zum Böhmegrund Sampling Date — January 17, 2002 Weather on Day of Sampling — Cloudy Weather on Day before Sampling — Cloudy Colour — Yellowish pH-Value — 8.20 Conductivity [µS/cm] — 397 DOC [mg C/L] — 7.3 DIC [mg C/L] — 9.9 Ammonium-N [mg N/L] — 0.141 Nitrate-N [mg N/L] — 12.52 o-Phosphate-P [mg P/L] — 0.095 Total Phosphate-P [mg P/L] — 0.393 Humic acids [mg/L] — 11.8 Suspended Matter* [mg/L] — 17.4 Total Hardness** [mg $CaCO_3$/L] — 91.3 Total Hardness** [mmol Ca+Mg/L] — 0.91 * = mean value of 2 measurements, **= mean value of 3 measurements • **European Rivers** In the EU Risk Assessment on Copper the DOC of European rivers was defined in the following range: **10th Percentile 2.6 mg/l; 50th Percentile 6.4 mg/l and 90th Percentile is 8.0 mg/l.**		

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Repeated freezing of river water to reduce microbial interaction which is an established method validated and applied to tertiary and primary amines since years. The results were accepted for assessment purposes (OECD and EU).

• Summary of the ecotoxcity test with river
Table 3.1.2 Available (Acute) River water Algae tests without and with worst case mitigation factor 10
<table>
<tr><td>n-Primary alkyl amines</td><td>ErC50 (72h) (mg/L)</td><td>ErC50 (72h) corr. (mg/L) Mitigation factor 10</td></tr>
<tr><td>Dodecan-1-amine</td><td>0.1</td><td>0.01</td></tr>
<tr><td>Coco alkyl amines</td><td>0.2</td><td>0.02</td></tr>
<tr><td>Tallow alkyl amines</td><td>0.4</td><td>0.04</td></tr>
<tr><td>Oleyl amine</td><td>0.5</td><td>0.05</td></tr>
</table>
Table 3.1.3 Available (Acute) River water Daphnia tests without and with worst case mitigation factor 10
<table>
<tr><td>n-Primary alkyl amines</td><td>EC50 (48h) (mg/L)</td><td>EC50 (48h) corr. (mg/L) Mitigation factor 10</td></tr>
<tr><td>Dodecan-1-amine</td><td>0.2</td><td>0.02</td></tr>
<tr><td>Coco alkyl amines</td><td>0.3</td><td>0.03</td></tr>
<tr><td>Tallow alkyl amines</td><td>n.a.</td><td>n.a.</td></tr>
<tr><td>Oleyl amine</td><td>1.0</td><td>0.1</td></tr>
</table>
The Algae ErC50 (72h, corr.) are in the range of 0.01 to 0.05 mg/l and the Daphnia EC50 (48h, corr.) are in the range of 0.02 to 0.1 mg/L.

• Consequences for mixtures
Because of the toxicity range given above a M factor of 10 has to be applied for mixtures under DSD and CLP.

3.2 Biodegradation and Metabolism
As biodegradation and biotransformation also influences bioaccumulation more details are given in this chapter than simply the results of 'ready biodegradability' of these amines.

3.2.1 Ready biodegradability in OECD 301x Standard tests
All 5 n-Primary alkyl amines (C12 to C18) covered by the ESR 93/793/EEC Environmental Risk Assessment and REACH are readily biodegradable (EU, 2008). Dodecan-1-amine as well as Hexadecan-1-amine belong to the C12 to C18 homologues as well and are also readily biodegradable.

For the Environmental Classification it can be concluded that all 7 n-Primary alkyl amines (C12 to C18) described in Table 2.1 are 'readily biodegradable'.

3.2.1 Degradation in Environmental Compartments
Based on the results from the OECD 301x Tests on 'Ready biodegradation' for the 7 n-Primary alkyl amines (C12 to C18) listed in Table 2.1 and an OECD 307 Study on the Aerobic degradation of 1-Hexadecanamine in soil, the Half-lives can be derived
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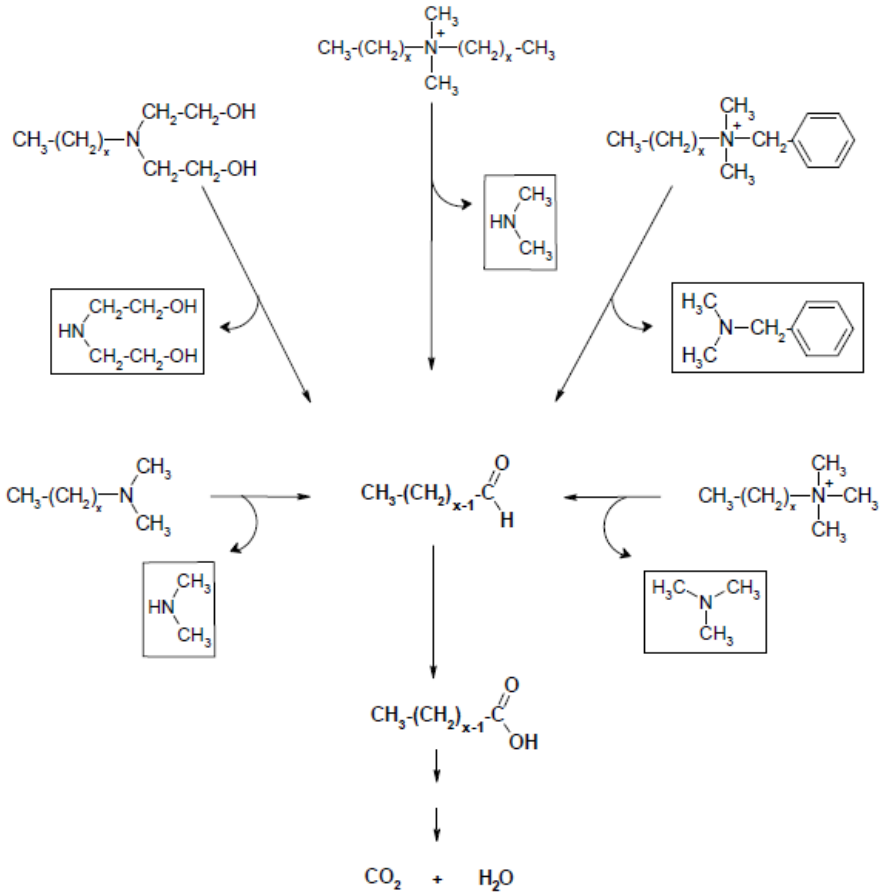
<tr><th>Date</th><th>Country/ Person/ Organisation/ MSCA</th><th>Comment</th><th>Response</th><th>Rapporteur's comment</th></tr>
<tr><td></td><td></td><td>
which are listed in Table 3.2.1.

Table 3.2.1 Degradation half-lives for C12-18 n-Primary alkyl amines
<table>
<tr><th>Compartment</th><th>Half-life at 12 deg C (d)</th><th>Test substance</th><th>Rational</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Freshwater</td><td>15d</td><td>C12-18 n-Prim. Alkyl amines</td><td>Estimation from ready test</td><td>REACH Guidance R.16.5</td></tr>
<tr><td>Soil</td><td>18.2</td><td>1-Hexadecanamine</td><td>OECD 307 median from 3 soils</td><td>Akzo & Clariant (2010)</td></tr>
<tr><td>Sediment</td><td>18.2</td><td>1-Hexadecanamine</td><td>Read across from OECD 307 soil study</td><td>Akzo & Clariant (2010)</td></tr>
</table>
The Half-lives given in Table 3.2.1 show that n-Primary alkyl amines (C12 to C18) are rapidly biodegraded in the Environmental compartments freshwater, soil and sediment.

3.2.2 Microbial metabolism
Primary, secondary, tertiary or quarternary alkyl amines are metabolized microbially following the same pathway. In scheme 3.2.2 the metabolic pathway of different tertiary and quaternary amines are shown as an example. The C-N bond of the long chain amine is cleaved by microbial oxidation to the corresponding aldehyde and di- or trimethyl amine. The aldehyde is oxidized to the corresponding fatty acid, which is further metabolized by beta-oxidation (van Ginkel, 2003). Cleavage of C-N bond leads to detoxification and formation natural and essential fatty acids.
</td><td></td><td></td></tr>
</table>

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Scheme 3.2.2 Metabolic pathway of different tertiary and quaternary amines  **3.2.3 Metabolism in fish** Metabolism in fish is an important factor influencing bioaccumulation. Nichols et al (2009) and Lawrence Burkhard (both Researchers of US EPA Office of Research & Development) have established a graph correlating log Kow and log BAF		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		(bioaccumulation factor) and demonstrating that with increasing metabolic rate in fish the log Kow/Log BCF curves were decreased. Fish metabolic rates km can either be measured in vivo or in vitro (Weisbrod et al, 2008) as well as estimated (Arnot, 2008). For 1-Hexadecanamine the km in carp was measured using an in vitro method (Bernhard et al, 2006). From these measurements two different km were derived for 1-Hexadecanamine: • km 0.152 1/d if only arterial blood supply is taken into account • km 1.024 1/d if arterial and portal blood supply is considered **3.3 Bioconcentration** Bioconcentration is one of the fate parameters which are difficult to measure or to estimate for amine containing cationic surfactants like the n-Primary alkyl amines (C12 to C18). These difficulties result from the inherent properties which are addressed in the next subchapter. Knowledge about these parameters may help in adapting methods to measure the fate parameter bioconcentration. The different methods are presented later in a Weight of Evidence approach. **3.3.1 Inherent properties of C12-18 n-Primary alkyl amines** The data given in this chapter can be found in detail in the REACH Registration Dossiers. ***Acid Base Properties of C12-18 n-Primary alkyl amines (C12 to C18)*** N-Primary alkyl amines are strong bases with a pKa of around 10.6 which protolyze with water to their corresponding ammonium salt. The pH in the environment e.g. 4-9 (OECD Guideline 111) influences how much of the unprotonated amine is available when compared with their corresponding ammonium salts. The fraction of base Xb at a given pH can be calculated with the following algorithm **Xb = Ka / (Ka + CH+) with Ka the acid constant and CH+ the proton conc.** The fraction of acid (ammonium salt) Xs is calculated from XB as Xs = 1-XB (Becke-Goehring, 1968). Table 3.3.1.1 summarizes the fractions of acid and base at pH 4 to 9. | pH	Acid fraction Xs	Base fraction Xb | |---|---|---| | 9 | 97.5 % | 2.500000% | | 7 | 99.975 % | 0.025000% | | 4 | 99.99997 % | 0.000003% | ***Water solubility and Critical Micelle Concentration*** **Table 3.3.1.2** Water solubility of unprotonated C12-18 n-Primary alkyl amines		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment

	Water solubility	References see REACH Dossier
Amines, tallow alkyl	0.12 mg/l at 25 °C (calc.) [10)] $7.89 \cdot 10^{-4}$ mg/L (calc. from literature)	Clariant, 1998 Industrial Applications of Surfactants, pg. 272
(Z)-Octadec-9-enylamine	insoluble at 25 °C [11)] 0.07639 at 25 °C (calculated) $6.20 \cdot 10^{-4}$ mg/L (calc. from literature)	CECA, 2000 Hoechst, 1996c Industrial Applications of Surfactants, pg. 272
Octadecylamine	insoluble at 25 °C [11)] 0.04875 mg/l at 25 °C (calc.) [9)] $5.59 \cdot 10^{-4}$ mg/L (calc. from literature)	Kao, 2000 Clariant, 2001a Industrial Applications of Surfactants, pg. 272
Amines, hydrogenated tallow alkyl	insoluble at 25 °C [11)] $7.98 \cdot 10^{-4}$ mg/L (calc. from literature)	Clariant, 2001b Industrial Applications of Surfactants, pg. 272
Amines, coco alkyl	insoluble at 25 °C [11)] $4.63 \cdot 10^{-3}$ mg/L (calc. from literature)	Clariant, 2001c Industrial Applications of Surfactants, pg. 272
Dodecylamine	3.71 mg/L (derived from literature)	Industrial Applications of Surfactants, pg. 272
Tetradecylamine	0.213 mg/L (derived from literature)	Industrial Applications of Surfactants, pg. 272
Hexadecylamine	0.01075 mg/L (derived from literature)	Industrial Applications of Surfactants, pg. 272

Whereas the free n-Primary alkyl amines do not have surfactant properties the corresponding ammonium salts do. The ammonium salts are so called cationic surfactants and due to their positive charge they behave differently with respect to water and octanol solubility as well as partitioning e.g. to solid surfaces.

The water solubility of protonated amines are best represented by measuring the Critical Micelle Concentration whereas for the free amines the classical methods for water solubility are applicable.

Table 3.3.1.3 Critical Micelle Concentration (CMC) to be used for Water solubility of protonated C12-18 n-Primary alkyl amines

DE: Thank you for the information. However, these values will not be mentioned in the CLH dossier, since they are not fully reliable or already given in the dossier. Since Dodecylamine,

<table>
<tr><th>Date</th><th>Country/ Person/ Organisation/ MSCA</th><th>Comment</th><th>Response</th><th>Rapporteur's comment</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th></th><th>Critical micelle concentration (CMC)</th><th>References see REACH Dossier</th></tr>
<tr><td>Dodecylamine hydrochloride</td><td>3.5 g/L at 25 °C</td><td>Clariant, 2008e</td></tr>
<tr><td>Tetradecylamine hydrochloride</td><td>0.69 g/L at 25 °C</td><td>Clariant, 2009r</td></tr>
<tr><td>Hexadecylamine hydrochloride</td><td>0.063 g/L at 25 °C</td><td>Clariant, 2010v</td></tr>
<tr><td>Octadecylamine hydrochloride</td><td>0.013 g/L at 25 °C</td><td>Clariant, 2010w</td></tr>
<tr><td>(Z)-Octadec-9-enylamine hydrochloride</td><td>0.038 g/L at 25 °C</td><td>Clariant, 2009q</td></tr>
</table>
Octanol solubility
Table 3.3.1.4 Octanol solubility of unprotonated and protonated C12-18 n-Primary alkyl amines
<table>
<tr><th></th><th>Octanol solubility</th><th>References see REACH Dossier</th></tr>
<tr><td>Dodecylamine</td><td>539 g/L at 20 °C</td><td>Clariant, 2009j</td></tr>
<tr><td>Tetradecylamine</td><td>310 g/L at 20 °C</td><td>Clariant, 2009k</td></tr>
<tr><td>Hexadecylamine</td><td>148 g/L at 20 °C</td><td>Clariant, 2009i</td></tr>
<tr><td>Octadecylamine</td><td>126 g/L at 20 °C</td><td>Clariant, 2009g</td></tr>
<tr><td>(Z)-Octadec-9-enylamine</td><td>813 g/L at 20 °C</td><td>Clariant, 2009h</td></tr>
<tr><td>Dodecylamine hydrochloride</td><td>27 g/L at 20 °C</td><td>Clariant, 2009l</td></tr>
<tr><td>Tetradecylamine hydrochloride</td><td>10 g/L at 20 °C</td><td>Clariant, 2009m</td></tr>
<tr><td>Hexadecylamine hydrochloride</td><td>7 g/L at 20 °C</td><td>Clariant, 2009n</td></tr>
<tr><td>Octadecylamine hydrochloride</td><td>6 g/L at 20 °C</td><td>Clariant, 2009o</td></tr>
<tr><td>(Z)-Octadec-9-enylamine hydrochloride</td><td>271 g/L at 20 °C</td><td>Clariant, 2009p</td></tr>
</table>
Partitioning between octanol and water
a) Log Kow
At environmental relevant pH e.g. 4 to 9 in water, unprotonated and protonated amine coexist with the protonated form being the pre-dominant (see paragraph on acid base properties before). Unprotonated n-Primary alkyl amines do not have surfactant properties. The protonated amines on the other hand are cationic surfactants having special phase behaviour. Measuring log Kow of mixtures of protonated and unprotonated amines with classical OECD methods may not always lead to valid results due to the complex phase behaviour of surfactants.
</td><td>Tetradecylamine and Hexadecylamine are not mentioned in the CLH report, the data for these substances were not added.</td><td></td></tr>
</table>

<table>
<tr><th>Date</th><th>Country/ Person/ Organisation/ MSCA</th><th>Comment</th><th>Response</th><th>Rapporteur's comment</th></tr>
<tr><td></td><td></td><td>
The log Kow of the unprotonated amine may be estimated with the Property estimation program US EPA KOWWIN (US EPA, 2008) as one way of circumventing the issues described before.

Table 3.3.1.5 Partitioning Octanol water Log Kow (calculated)
<table>
<tr><th></th><th>Partitioning Octanol water log Kow (calculated)</th><th>References see REACH Dossier</th></tr>
<tr><td>Dodecylamine</td><td>4.7 (calc. with US EPA KowWIN)</td><td>Clariant, 2010ar</td></tr>
<tr><td>Tetradecylamine</td><td>5.7 (calc. with US EPA KowWIN)</td><td>Clariant, 2010as</td></tr>
<tr><td>Hexadecylamine</td><td>6.7 (calc. with US EPA KowWIN)</td><td>Clariant, 2010at</td></tr>
<tr><td>Octadecylamine</td><td>7.7 (calc. with US EPA KowWIN)</td><td>Clariant, 2010au</td></tr>
<tr><td>(Z)-Octadec-9-enylamine</td><td>7.5 (calc. with US EPA KowWIN)</td><td>Clariant, 2010av</td></tr>
</table>
b) Log Coctanol / Cwater

Unprotonated amines
Instead of estimating the log Kow of the pure unprotonated amines, the quotient of the octanol and water solubility of the unprotonated amine may be used instead (see table 3.3.1.6). The Log Coctanol / Cwater values for the n-Primary alkyl amines (C12 to C18) are by 0.4 to 0.7 log units higher than the corresponding value of Log Kow estimated with US EPA KOWWIN (US EPA, 2008) see Table 3.3.1.5. A likely explanation for this higher value is that a log Kow is measured in water saturated n-Octanol and n-Octanol saturated water which decreases the solubility of the Unprotonated amine in the octanol phase and increases the solubility in the aqueous phase.

Table 3.3.1.6 Partitioning Octanol water Log Coctanol / Cwater (unprotonated amines)
<table>
<tr><th></th><th>Partitioning Octanol water log Kow (calculated from log$C_{octanol}/C_{water}$)</th><th>References see REACH Dossier</th></tr>
<tr><td>Dodecylamine</td><td>5.2 (calculated from solubility)</td><td>Clariant, 2010ac</td></tr>
<tr><td>Tetradecylamine</td><td>6.2 (calculated from solubility)</td><td>Clariant, 2010ad</td></tr>
<tr><td>Hexadecylamine</td><td>7.1 (calculated from solubility)</td><td>Clariant, 2010ae</td></tr>
<tr><td>Octadecylamine</td><td>8.4 (calculated from solubility)</td><td>Clariant, 2010af</td></tr>
<tr><td>(Z)-Octadec-9-enylamine</td><td>9.2 (calculated from solubility)</td><td>Clariant, 2010ag</td></tr>
</table>
Protonated amines
For protonated amines no reliable property estimation method for log Kow is available. Alternatively the octanol/ water partitioning could be calculated from either octanol solubility or water solubility of the protonated amines (Log Coctanol / Cwater. It is important to note that the observed Log Coctanol / Cwater of the protonated n-Primary alkyl amines (Table 3.3.1.7) is between 4 to 6 orders of magnitude lower than the Log Coctanol / Cwater of the unprotonated amines (Table 3.3.1.6). This is an indication that the protonated amines have a low tendency to partition to lipids and may therefore have a reduced potential to be taken up into biota. This is in line with the findings that ionic compounds have a reduced bioaccumulation potential (US EPA BCFWIN, Underlying database for BCF QSAR, US EPA, 2000).
</td><td>DE: Thank you for the information. However, these values will not be mentioned in the CLH dossier, since they are not fully reliable or already given in the dossier. Since Dodecylamine, Tetradecylamine and Hexadecylamine are not mentioned in the</td><td></td></tr>
</table>

<table>
<tr><th>Date</th><th>Country/ Person/ Organisation/ MSCA</th><th>Comment</th><th>Response</th><th>Rapporteur's comment</th></tr>
<tr><td></td><td></td><td>
Table 3.3.1.7 Partitioning Octanol water Log Coctanol / Cwater (protonated amines)
<table>
<tr><th></th><th>Partitioning Octanol water log Kow (calculated from log$C_{octanol}/C_{water}$)</th><th>References see REACH Dossier</th></tr>
<tr><td>Dodecylamine hydrochloride</td><td>0.9 (calculated from solubility)</td><td>Clariant, 2010am</td></tr>
<tr><td>Tetradecylamine hydrochloride</td><td>1.2 (calculated from solubility)</td><td>Clariant, 2010an</td></tr>
<tr><td>Hexadecylamine hydrochloride</td><td>2.1 (calculated from solubility)</td><td>Clariant, 2010ao</td></tr>
<tr><td>Octadecylamine hydrochloride</td><td>2.7 (calculated from solubility)</td><td>Clariant, 2010ap</td></tr>
<tr><td>(Z)-Octadec-9-enylamine hydrochloride</td><td>3.9 (calculated from solubility)</td><td>Clariant, 2010aq</td></tr>
</table>
c) Log D apparent Kow for weak electrolytes (acid and base fractions considered)
Fu et al (2009) have published a model which can estimate the BCF of acid and bases as function of the pH (see later). This model describes how to estimate the apparent Kow also called D for weak electrolytes. The fraction of the unprotonated amine fn can be calculated by the Henderson- Haselbalch equation
fn = 1 / (1+10i(pKa-pH)) with i = 1 for bases
The apparent Kow for weak electrolytes also called D can be calculated by
D = fn * Kow (unprotonated) + fd * Kow (protonated)
Kow (protonated) can be either calculated by
Log Kow (protonated) = Log Kow (unprotonated) – 3.5 (1)
Or the measured Log Coct/Cwater for the protonated can be used.

Table 3.3.1.8 Log Kow (protonated) calculated according equation (1) or using measured Log Coct/Cwater
<table>
<tr><th></th><th>Log Kow according eq. (1)</th><th>Log C_{oct}/C_{water} (see Table 3.3.7)</th></tr>
<tr><td>Dodecylamine hydrochloride</td><td>1.2</td><td>0.9 (calculated from solubility)</td></tr>
<tr><td>Tetradecylamine hydrochloride</td><td>2.2</td><td>1.2 (calculated from solubility)</td></tr>
<tr><td>Hexadecylamine hydrochloride</td><td>3.2</td><td>2.1 (calculated from solubility)</td></tr>
<tr><td>Octadecylamine hydrochloride</td><td>4.2</td><td>2.7 (calculated from solubility)</td></tr>
</table>
The measured values are lower than the calculated ones according equation (1).

3.3.2 Measuring the BCF using in vivo methods
In principle in vivo methods to measure the BCF are prefered as they address the Adsorption, Distribution, Metabolism and Excretion (so called ADME process) of the test substance.

Measuring the BCF with a flow-through Fish test
</td><td>CLH report, the data for these substances were not added.</td><td></td></tr>
</table>

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		For the in vivo measurement of the BCF in fish under flow through conditions the OECD Guideline 305 exists. This Guideline is currently updated. Unfortunately the OECD 305 gives no Guidance how to deal with cationic surfactants in this test. The following issues prevent that a reliable BCF can be determined: • There is no measurement technique available to determine the truly dissolved substance concentration. APAG has initiated a 5 year Research program (APAG 2008) to develop a Solid phase microextraction (SPME) method for cationic surfactant to allow solubility measurements. This project aims also to develop a mechanistic model for the partitioning behaviour of these substances. • Because of the strong sorption of Cationic surfactants to the glass surfaces and tubings of the test setting a reliable and constant substance concentration in the test water during the flow through test cannot be obtained. This is further complicated by the fact that organic matter from the fish is present in the test system which causes biodegradation as these cationics are readily biodegradable. • As the fish mucous is negatively charged the fish surface is coated slowly with the test substance by ion exchange. This coating will not occur under environmental conditions as the cationic surfactant is to a large extent bound to dissolved DOC or suspended matter present in surface water. In addition the slow coating of the fish mucous during the OECD 305 test prevents that an equilibrium between uptake and depuration can be achieved in a reasonable time frame. Although APAG was aware of these test issues it was agreed among Industry and Authorities to give such a test a try. The effort for setting up the test was huge. However the issues listed above did not allow to derive any reliable Bioconcentration factor. ***Critical Body Burden (CBB) Approach*** To link the internal substance concentrations in the tissue with the external derived effect data is another approach to estimate the Bioconcentration factor BCF. APAG has carried out 21d (Chronic) Daphnia reproduction studies in river water with the following commercial Primary alkyl amines: Coco alkyl amines (C12-14 alkyl amines), Tallow alkyl amines (C16-18 alkyl amines) and Oleylamine (C18 (unsaturated) alkyl amine. For all three amines the OECreproduction, river water is 13 µg/L (nominal) and EC50reproduction, river water is 0.34, 0.24 and 0.27 mg/L respectively. The recovery of the 0.5 mg/L test solutions were 20%, 36.8% and 36.5% respectively (4 fresh and 4 old test solutions). Daphnia is the most sensitive species in the aquatic ecotoxicity tests. Chronic fish data are not available as fish is less sensitive to the n- Primary alkyl amines (C12 to C18). Thomson & Stewart (2003) have correlated the Critical Body Burden (CBB) with BCF times NOEC. Although CBB may differ among species a conservative Critical Body Burden (CBB) of 2*Mol weight [µg/L] may be used as derived in the 'REACH Guidance R.11 PBT Assessment' (EU, 2008). This CBB covers chronic effects and the BCF for n-Primary alkyl amines (C12 to C18) can be calculated according the following algorithm (Thomson & Stewart, 2003). The mitigating effect of the river water tests is corrected by a factor of 5 (estimated from available ecotoxicity data) which means that the NOECreprod, riverwater, corr would be 2.6 µg/L **BCF = CBB / NOECreproduction, river water, corr** **Table 3.3.2.1** CBB, NOECreprod, corr and the BCF of C12 to C18 alkyl amines for Daphnia		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment

Commerical amine	Chain length	Mol weight (g/Mol)	Critcal Body Burden (µg/L)	Measured NOEC corr (µg/L)	BCF (calc.)
Coco					
	C12	185.5	371	2.6	143
	C14	213.5	427	2.6	164
Tallow					
	C16	241.5	483	2.6	186
	C18	296.5	593	2.6	228
Oleyl					
	C18	296.5	593	2.6	228
	C18'	292.5	585	2.6	225

The average BCF for Daphnia of all C12 to C18 amines is in the range of 143-225 with an average of ca. 180. Daphnia is exposed via water and food e.g. algae and what is measured is a BAF instead of a BCF which can be considered as a worst case. Daphnia is not a fish but it seems reasonable that the low bioaccumulation results for Daphnia may be an indicator for the bioconcentration potential of Primary alkyl amines in the aquatic compartment in general.

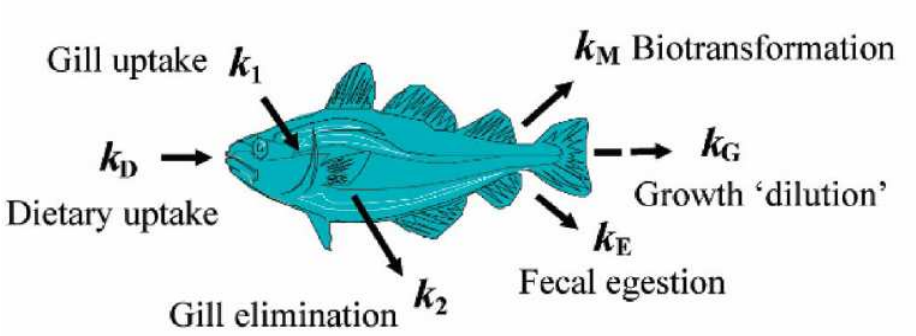
3.3.3 Predictive approaches for the BCF Assessment

Only those predictive approaches were considered which at least cover metabolism in biota and/or the protolysis of the amines. No approaches are addressed which correlate BCF with partitioning properties only.

3.3.3.1 Predictive approaches for the BCF Assessment considering Metabolism

ADME models and measured Fish metabolic rates

ADME Models address all important uptake and depuration pathways as shown in the figure below.



<table>
<tr><th>Date</th><th>Country/ Person/ Organisation/ MSCA</th><th>Comment</th><th>Response</th><th>Rapporteur's comment</th></tr>
<tr><td></td><td></td><td>
The ADME Process can be described by the BCF Model from Arnot & Gobas (2003).
BCF = (1 – LB) + (kuptake * fdiss / (kelimin + kegestion + kgrowth + kmetabol.))

LB = Lipid fraction in organism
Kuptake = uptake rate (estimated by: 1/(0.01 + 1/Kow)* Weight0.4)
fdiss = fraction of dissolved substance
kelimin = elimination rate (estimated by: kuptake / LB * Kow)
kegestion = faecal egestion rate (estimated by: 0.02*Weight-0.15* e-0.06T/(5.1*10-8*Kow+2)*0.125
kgrowth = 0.0005*Weight-0.2
kmetabol. = measured rate
This model was applied to the unprotonated C12 to C18 n-Primary alkyl amines (C12 to C18). Table 2 shows the input parameter for the model for the C16 amine (1-Hexadecylamine). It is assumed that the fish km is the same for all amine homologues (seems reasonable due to the same primary degradation of the C-N bond).These data were adapted for the remaining amines and used for the BCF calculation as well. Table 3 summarizes the ADME results for all C12 to C18 amines. The BCF were calculated using estimated log Kow of the free amines (US KOWWIN) and measured log Coct/Cwater. The differences are marginal.

Table 3.3.3.3.1 Parameters used for C16 amine (1-Hexadecylamine) in ADME model for fish
<table>
<tr><th>Parameter</th><th>Value used in modelling</th><th>Remark</th></tr>
<tr><td>Log K_{ow}</td><td>6.7</td><td>Estimated with US EPA KOWWIN V. 1.67 (US EPA, 2008b)</td></tr>
<tr><td>L_B (lipid fraction)</td><td>0.2</td><td>Standard in model</td></tr>
<tr><td>Weight of fish (kg)</td><td>0.438</td><td>Av. Fish weight in study for carp metabolic rate (Bernard et al., 2006)</td></tr>
<tr><td>Temperature (deg C)</td><td>12</td><td>REACH Guidance R.16.4.3.1</td></tr>
<tr><td>$f_{freely\ disss}$ (freely dissolved fraction)</td><td>0.2</td><td>Estim. from the differences in ecotox measured in tap & in river water</td></tr>
<tr><td>$k_{metabolism}$ (1/d)</td><td>0.152</td><td>Lowest value from in vitro study (Bernhard et al, 2006) see also Chapter 3.2.3</td></tr>
</table>
Table 3.3.3.3.2 Summary of BCF for the unprotonated and protonated C12 to C18 amines from the ADME model for Fish (Arnot & Gobas, 2003) using the appropriate substance data
</td><td></td><td></td></tr>
</table>

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment

	UNPROTONATED AMINE		PROTONATED AMINE
Chain length n-Primary alkyl amines	BCF using Log K_{ow} (L/kg) from KOWWIN see Table 3.3.1.5	BCF using measured Log C_{oct}/C_{water} (L/kg) see Table 3.3.1.6	BCF using measured Log C_{oct}/C_{water} (L/kg) see Table 3.3.1.7
C12	162	168	1.1
C14	172	173	1.4
C16	173	173	5.6
C18	174	174	18.4

The BCF for the **unprotonated** n-Primary alkyl amines (C12 to C18) are low and in the range of 168 to 174 L/kg wwt.
When using the ADME Model to calculate the BCF for the **protonated** n-Primary alkyl amines (C12 to C18) using the Log Coct/Cwater (Table 3.3.1.7) very low BCF (1.1-18.4 L/kg wwt.) were obtained. These low values are similar to the very low BCF values of Quats e.g. DODMAC BCF 13.1 L/kg which cannot be deprotonated. But it is unclear if the ADME model can predicted the BCF of Cationics and one has to be very cautious when interpreting these BCF for the protonated amines.

3.3.3.2 Predictive approaches for the BCF Assessment without considering Metabolism

Use of a Model which can predict the BCF for acids and bases in equilbrium

Fu et al (2009) have published a model which can estimate the BCF of acid and bases as function of the pH. The fraction of the unprotonated amine fn can be calculated by the Henderson-Haselbalch equation

fn = 1 / (1+10i(pKa-pH)) with i = 1 for bases

The apparent Kow for weak electrolytes also called D can be calculated by

D = fn * Kow (unprotonated) + fd * Kow (protonated)

Kow (protonated) can be either calculated by

Log Kow (protonated) = Log Kow (unprotonated) – 3.5

or the measured Log Coct/Cwater for the protonated can be used. Fu et al. analyzed available data for strong bases and found the following regression

Log BCF = 0.24 Log D + 0.87

For the C16 amine the BCF can be estamated as function of pH 4, 7 and 9

Table 3.3.3.2 BCF as function of pH for the C16 amine

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment

	BCF		
	pH4	pH7	pH9
C16 amine	43	50	124

Conclusion:
The model of Fu et al (2009) is the only one which can address the BCF of acids and bases as function of the pH but it cannot be judged if cationic surfactants were included in the training set of the model. The model can also not address metabolism in e.g. fish.

3.3.4. Weight of Evidence Approach for C12-C18 n-Primary alkyl amines
None of the approaches described in this chapter and used to derive the BCF of n-Primary alkyl amines (C12 to C18) delivers results which addresses the ADME process for the unprotonated and the protonated amine using measured data. Therefore a Weight of Evidence Approach was chosen as the most sensible one.
1) As explained in Chapter 3.3.2 the inherent properties of amine containing cationic surfactant create test issues which cannot be overcome using the test design for an OECD 305 BCF test. The result from a preliminary test is invalid as several validity criteria of the test guideline could not be met e.g. constant water concentration, equilibrium etc.
2) From the NOEC for reproduction from 21d Daphnia tests BCF were calculated using the Critical Body Burden approach. The BCF values for the n-Primary alkyl amines (C12 to C18) are in the range of 143-225.
3) The ADME model of Arnot & Gobas (2003) can address the ADME process most likely only for the unprotonated amine. The values calculated for the protonated amines (see Table 3.3.3.3.2) are illustrative only as the applicabilitiy of the model to cationics is unknown.The measured in vitro metabolic rate km for 1-Hexadecanamine in fish was used to predict the BCF fish for the different unprotonated amines assuming the same metabolic rate (same deamination pathway to fatty acids). It is important to note that for the calculation of the BCF, the lower of the two measured metabolic rates was used as a worst case (see Chapter 3.2.3).
4) The model of Fu et al (2009) is the only model which can address the coexisting protonated and unprotonated C16 amine as function of pH. Unfortunately it does address only the Adsorption of the ADME process and does not cover the important metabolism of the amines. In addition it is not known if the approach is valid for cationic surfactants.
As no data are available to establish a Critical Body Burden Approach for fish, the ADME Model of Arnot & Gobas (2003) using in vitro fish metabolic rates for the model compound Hexadecan-1-amine seems to be to date the most reliable approach to derive a BCF fish for the n-Primary alkyl amines (C12 to C18). The BCFs fish calculated with the ADME Model are low. In addition the BCF for Daphnia using the Critical Body Burden Approach are low as well and are not in conflict with the BCF fish derived with ADME model.

Overall conclusion:
1-Hexadecanamine is a model compound for the n-Primary alkyl amines (C12 to C18).
Therefore it is proposed to use **for the n-Primary alkyl amines (C12 to C18) a BCF of 173 L/kg** as estimated by the ADME Model of Arnot & Gobas (2003).

4. Classification approach

4.1 Ecotoxicity
Based on the inherent properties described in Chapter 3.1
Acute and chronic river water tests with algae and daphnia show effect values >=0.01 mg/L (M factor 10 for mixtures)
Which leads to a Classification

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		DSD 67/548/EEC N, R50 (M factor 10 for mixtures) **CLP 2008/272/EC Acute (short-term) aquatic hazard,** **H400 (M factor 10 for mixtures)** **4.2 Potential long-term hazards** **4.2.1 Ready biodegradability** All n-Primary alkyl amines (C12 to C18) are 'readily biodegradable' **4.2.2 Bioconcentration** Based on a Weight of Evidence Approach described in the Chapter before a BCF fish of 173 L/kg was derived to be used for n-Primary alkyl amines (C12 to C18). This value does formally lead to a R53 under DSD 67/548/EEC because of the very low BCF critieria of 100 L/kg. Based on the BCF critieria of 500 for CLP no long-term effect has to be assigned. In order not to confuse the customer the more realistic BCF criteria of the CLP should be taken into account to avoid a R53 classification which would mean long-term effects which are not present in reality. It is also important to note that recent criteria for PBT and vPvB use BCF/BAF of >2000 respectively >5000 as threshold which do reflect the state of science whereas the classification criteria for BCF in CLP and especially DSD are overly conservative and unrealistic. **4.3 Overall classification** **Dangerous Substance Directive 67/548/EEC** N, R50 R53 is not assigned to avoid a conflict to the CLP classifcation (see explanation before) M factor 10 for mixtures **Classification, Labelling, Packaging Regulation 2008/272/EC** Acute (short-term) aquatic hazard, H400, M factor 10 for mixtures **References** *Akzo & Clariant (2010)* 1-Hexadecanamine, Degradation in Three Soils Incubated under Aerobic Conditions, Harlan, Report No. C95393, *APAG (2008)* Research Project 'Towards a better Understanding of the bioavailability and Partitioning behaviour of Cationic surfactants (Kai-Uwe Goss & Steven Droge, UFZ Leipzig and Joop Hermens, University of Utrecht) *APAG (2010)* DSD & CLP Classification Guidance for Cationic surfactants containing amine Structure(s) *Arnot (2008)* Guidance for Evaluating in vivo fish bioaccumulation data, IEAM 4,2, 139-155 *Arnot & Gobas (2003)* A generic model for assessing the bioaccumulation potential of organic chemicals in aquatic food webs, QSAR Comb. Sci. 22:337-345 *Becke-Goehring (1968)* Einführung in die Theorie der Quantitativen Analyse, Verlag Theodor Steinkopf, Dresden, 1968 *Bernhard et al (2006)* Determination of In vitro Biotransformation of C16 amine in Fish Hepatocyte Suspension, ERASM, 2006, www.erasm.org *CEFIC (2008)* The Relevance of the 10d Window in the Context of the Assessment of ready Biodegradability for Surfactants (March 2008) *ECETOC (2003)* Environmental Risk Assessment of Difficult Substances, Technical Report No. 88 *EU (2008)* REACH Guidance R.11 PBT and vPvB Assessment, Chapter R.11.1.4. *Fu et al (2009)* Methods for estimating the bioconcentration factor of ionizable organic chemicals, ETC. 28, 7, 1372-1379		

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Nichols et al (2009) Bioaccumulation Assessment using Predictive Approaches, IEAM, 5, 4, 577-597 *Richterich et al. (2001)* The time-window an inadequate criterion for the ready biodegradability assessment of technical surfactants. Chemosphere 44, 1649-1654 *Thomson & Stewart (2003)* Critical Body Burdens: A review of the literature and identification of experimental data requirements, BL7549/B, CEFIC LRI *US EPA (2000)* US EPA QSAR Model for BCF (BCFWIN), http://www.epa.gov/oppt/exposure/pubs/episuite.htm *US EPA (2008a)* Test Guidelines OPPTS 835.3140, Ready Biodegradability – CO2 in sealed vessels (Headspace test), page 9 *US EPA (2008b)* US EPA QSAR Model for Kow (KOWWIN) http://www.epa.gov/oppt/exposure/pubs/episuite.htm *Weisbrod et al (2009)* The state of in vitro science for use in Bioaccumulation assessment for fish, Env. Tox. Chem. 28, 1, 86-96		

Attachment:

APAG Primary Fatty Amine Consortium, Germany, *CLH_Dossier-Comments_Tallow.pdf*
Submitted during the public consultation, includes confidential information.

APAG Primary Fatty Amine Consortium, Germany, *Specific_comments_Tallow.pdf*
Submitted after the public consultation as requested by ECHA.

APAG Primary Fatty Amine Consortium, Germany, *Attachment_2_CLH_Position_Paper.pdf*
Submitted after the public consultation as requested by ECHA.

APAG Primary Fatty Amine Consortium, Germany, *Cover_Letter.pdf*
Submitted after the public consultation as requested by ECHA.

Appendix 1 - Response of the German CA to the comments provided by the UK CA with respect to skin and respiratory irritation

Skin irritation

The comment on missing individual scores and resulting lack of transparency with respect to fulfilment of classification criteria is justified. We have revised the CLH report accordingly:

Individual animal data demonstrating that the classification criteria were met both under DSD and CLP were included for the two studies rated as 'key studies' in our proposal, i. e. Liggett & Parcell 1984 (Huntingdon Research Centre) for hydrogenated tallow alkyl amines and Kreiling & Jung 1989 (Hoechst AG) for octadecylamine. However, we refrained from adding this information for all of the studies listed, as this would have meant an excessive additional workload without any further regulatory benefit.

Respiratory tract

We noticed that the description of the relevant effects observed in the acute inhalation toxicity study with coco alkyl amine was misleading: the phrase '…but these findings were not rated as compound-related histomorphologic alterations' was intended to refer only to the observed kidney effects.

Thus we have corrected this sentence accordingly ('…the latter finding was not rated…'). In addition, the relevant findings with regard to respiratory irritation were underlined in the text (section 5.2.2.1): '[…]After 40 minutes, several animals exhibited a slight irritation around the muzzle.[…] After 30 minutes, several animals showed signs of irritation, were preening, and exhibited a nasal discharge. At the end of the one-hour exposure, all rats showed mild to severe irritation around the muzzle and had reddish areas on the fur.[…] Microscopic evaluation of selected tissues from the rats in the 0.099 mg/L dose group included minimal to slight peribronchial lymphoid hyperplasia present in the lung […]'.

The full reasoning behind the proposal for R37 is given in section 5.3.3. of the CLH report and we believe that no change or further explanation is required there.

In addition, to our knowledge and in contrast to eye irritation/serious damage, respiratory irritation is not implicitly covered by a classification for corrosivity (which arguably should be the case). Whether or not for the corrosive amines even EUH071 should be assigned under CLP is not clear to us. It is suggested that this issue be discussed by RAC.

Appendix 2 - Response of the German CA to the comments provided by Industry (APAG consortium) with respect to Human Health endpoints

Below, for the sake of greater clarity, we have addressed industry's comments in a summarised way, for all five amines together, and grouped according to the main issues raised:

General comments

When the CLP Regulation went into force, it was decided that for dossiers previously discussed, but not finalised at the former Technical Committee for Classification & Labelling (TC C&L), MSCAs should have the opportunity to re-submit the corresponding dossiers as CLH proposals under CLP, using the format specified in Annex XV of the REACH Regulation. A simplified procedure was foreseen if the dossiers were submitted by the end of 2009.

As mentioned in the CLH report, and in contrast to classification for environmental endpoints, no formal agreement on the classification for human health endpoints had been reached at TC NES level. As a consequence, the RARs previously prepared for the primary alkyl amines by the German CA under the 'old' chemicals legislation had to be converted into CLH reports. In this context, in autumn 2009, a partial re-evaluation of the underlying data base was performed which resulted in a number of amendments/corrections of the text as well as a slight extension of the classification proposal with respect to respiratory irritation (read-across from coco alkyl amines to the rest of the group).

The focus of the original RAR lay on a full description of the toxicological data base for the five amines under question, including data not directly linked to the classification proposal. The German CA decided to leave this information in the dossier, among other reasons, because it was felt that it could further support the grouping approach in general.

The German CA noted that some of Industry's comments relate to text passages which do not relate to the classification proposal as such. Consequently, these comments are also not relevant for the further discussion on harmonised classification and labelling and, in general, are therefore not dealt with in our response, in line with the following considerations:

- In contrast to the evaluation process for Existing Substances, discussion under the CLH process should only focus on the proposed Classification & Labelling.
- Industry's position has been documented already in this RCOM table. In the end, both the MSCA's CLH report and the comments received during the CLH process present the same qualitative level of 'evidence': they do not by themselves constitute any legally binding documents, whereas the final RAC opinion will only contain information relevant to C & L.

Based on industry's comments, we have re-read our report and have revised our position where we found it appropriate. In our view the remaining discussion should focus only on those sections relevant for C & L.
Back in 2009, when the new/transferred CLH reports were generated, no registration information under REACH was available and consequently, no such information could have been considered in the preparation of the dossiers. However, in the course of preparing this response we have performed a quick review of the registration dossiers available for the substances indicated in the table provided by Industry. While at this stage no decision was made whether or not the substances registered under a different name and CAS no. were really identical to those treated in our own CLH-reports, the results of this analysis were as follows:

- Apparently, with the new registrations, no toxicity studies for acute toxicity, skin irritation/corrosion, eye irritation, inhalation toxicity, or repeat-dose toxicity were submitted which have not been discussed in our CLH dossiers.

- With respect to human health endpoints, the registrants' classification and labelling proposals deviate from those of the German CA (after amendments based on Industry's comments, cf. below) only in two aspects, i. e.

    - whether or not also the non-corrosive amines should be classified as respiratory irritants and

    - whether coco alkyl amines should be classified as Skin Corr 1A or 1B under the CLP regulation.

  N.b.: both points are explicitly addressed in this response.

- The only other new data relevant to the text of the CLH report pertain to issues not directly relevant for the classification/labelling proposed by the German CA (i. e. measurements of viscosity or solubility). However, as these issues relate to endpoints where there was some initial concern about the potential need for classification (skin sensitisation, aspiration hazard), we have addressed them below.

- It is noted that due to their different identity, our CLH proposal will not directly affect the substances newly registered by APAG. In our view, though, it is Industry's responsibility to adapt the respective entries in the C & L Inventory accordingly, if they consider their substances identical to those treated in our dossier. Depending on whether Inventory entries really are in agreement with each other and our proposal, this could obviate the need for a future extension of this CLH proposal also to the newly registered substances.

Justification for community-wide action

The German CA has seen the need for community-wide action based on the following reasoning:

'[…] Each registrant for any of the substances in this report will most likely only have access to a limited subset of the data presented here. In such a scenario, contradictory entries in the inventory (which would THEN trigger the need for CLH) can be expected with high probability. The current CLH proposal therefore constitutes an efficient way of assuring a high quality standard by proactively evading conflicting C & L and - as a consequence - avoiding time-consuming follow-up work.'

APAG questions the need for a harmonised classification/labelling for the primary amines, based on the following arguments:

- their consortium has submitted registration dossiers for all five substances (albeit under a different identity with respect to four of them); all partners of the SIEF/consortium thus had access to the same data and hence
- all partners of the consortium have submitted identical self-classifications to the C &L inventory.

For the purpose of verification of these arguments on a more general level, the German CA asked ECHA for an advance excerpt from the not yet publically available C & L inventory with respect to Industry's self-classification of the substance 61790-33-8 (Amines, tallow alkyl).

Table A2-1 below demonstrates the remarkable spectrum of different self-classifications submitted for this substance as well as the distribution of different combinations of classifications over a total of 29 entries.

Table A2-1: Overview of self-classifications for the substance Amines, tallow alkyl (CAS 61790-33-8, advance excerpt from the C & L Inventory)

Acute Tox 4 H302	Acute Tox 4 H312	Acute Tox 4 H332	Skin Irrit 2 H315	Skin Corr 1B H314	Skin Corr 1A H314	Skin Sens 1 H317	Eye Irrit 2 H319	Eye Dam 1 H318	STOT SE 3 H335	STOT RE 2 H373	Aquatic Acute 1 H400	Aquatic Chronic 1 H410	Met. Corr 1 H290	Number of entries
														1
X														1
			X			X								1
			X				X		X					1
X				X										2
X				X					X	X				1
X				X					X	X	X			2
					X									2

X					X									1
					X						X			1
X					X						X			11
X					X	X		X			X			3
X	X	X			X	X		X				X		1
X					X				X	X		X	X	1

Based on these findings, the German CA sees its line of argumentation and thus, the need for community-wide action, confirmed.

Human health-related endpoints

Classification of (Z)-Octa-decen-9-ylamine as R35 or R34

APAG rightfully objects to the proposal of R35 on page 7. We apologize for this typing error, which has now been corrected. Indeed R34/Skin Irrit 1B is applicable for (Z)-octadec-9-enylamine, as proposed throughout the rest of the text and the technical dossier.

Translation of R35 into Skin Corr 1A or 1B

APAG in their comment correctly note that R35 under the DSD does not automatically translate into Skin Corr 1A. Instead they propose that all three corrosive amines should be classified as Skin Corr 1B, as in many of the evaluated studies following a 3 min exposure, responses indicative of corrosivity were only observed more than one hour post-exposure.

Upon re-evaluation of the respective study reports, the German CA concedes that the comment by APAG is justified for Amines, tallow alkyl. Therefore the classification proposal for this substance with respect to the CLP regulation is changed to Skin Corr 1B.

For Amines, coco alkyl, one of the key studies (Markert/Weigand, Hoechst AG 1984) shows that one animal displayed dermal symptoms indicative of corrosivity already 30-60 min following three minute exposure. Thus, in accordance with the CLP criteria, classification as Skin Corr 1A is maintained. However, the point is clarified under section 5.3.1.1 of the CLH report.

Classification proposal for respiratory irritation

While both under CLP and DSD corrosivity is explicitly mentioned to imply a potential to cause eye damage, a similar phrase was not found for respiratory irritation. Arguably this is an inconsistency in the regulatory framework, but at least historically, some cases can be found where classification for both corrosivity and respiratory irritation was assigned: We searched Annex VI of the CLP regulation and found

- 273 substances classified as R34 of which 8 substances were also classified as R37,
- 86 substances classified as R35 of which 3 substances were also classified as R37.

The reasoning behind the proposal to classify all amines (not only the corrosive ones) included in the group approach for respiratory irritation is presented in the CLH report under section 5.3.3. We still find it to provide sufficiently strong support for the classification proposal.

In other words, from a toxicological point of view, we believe classification with R37/STOT SE 3 is justified for all amines under question. Arguably, rather the regulatory need to assign this classification in the presence of corrosivity might be considered low (whereas for the 'only' irritant amines (and in contrast to Industry's position) we think it should be assigned). We suggest that this issue be discussed by RAC.

STOT RE 2 (Immunotoxicity)

Industry's comment with respect to immunotoxicity is noted, but our proposal is maintained.

Skin sensitisation

The German CA still is of the opinion that both available studies were not performed fully to guideline standards and, therefore, cannot serve as a full proof of the absence of a sensitising potential. It is worth noting that even some submitters to the Classification & Labelling Inventory found it appropriate to classify tallow alkyl amines for skin sensitisation (cf. Table A2-1 above).

Thus, whereas our conclusions on these studies basically remain unchanged, the text in the CLH report was slightly changed to clarify the experimental deficiencies found.

Aspiration hazard

In our understanding, Industry's comments are rather supporting the idea of classifying for aspiration hazard than the opposite:

- In their comment, APAG characterises the lung effects as 'indirect local effects due to secondary inhalation of foamy particles instilled originally into the stomach (reflux-phenomenon)'. We find this definition not to be in contradiction with the definition of aspiration hazard in the CLP regulation:

  '[…] 'Aspiration' means the entry of a liquid or solid substance or mixture directly through the oral or nasal cavity, or indirectly from vomiting, into the trachea and lower respiratory system.[…]'

- The new data presented at the example of octadecylamine result in a dynamic viscosity of 4.63 x 10^{-6} m^2/s or 4.63 mm^2/s at 60 °C, which is even lower than the values estimated in our report. As compared to the classification thresholds, the criteria of both the DSD (< 7 mm^2/s) and CLP (< 20.5 mm^2/s) are clearly met, even if it is granted that at 40 °C, a slightly higher value might have been obtained than at 60 °C.

Under both the DSD and CLP, classification for aspiration hazard is called for in two different cases: a) based on practical experience in humans (not available for the primary alkyl amines) or b) if certain technical criteria are met (which is the case, cf. above) AND the substance is a hydrocarbon. As stated in the CLH report, especially the long-chain fatty amines such as octadecylamine feature a spacious hydrocarbon moiety while at the same time not being hydrocarbons in the narrow sense of the word (i. e. consisting only of carbon and hydrogen) and thus not fulfilling the classification criterion exactly. N.b. currently at least three of the 189 substances classified for aspiration in Annex VI to the CLP regulation are not pure hydrocarbons, i. e. 1.3-dichloropropene, 2-methyl-5-*tert*-butylthiophenol, and http://ecb.jrc.ec.europa.eu/classification-labelling/clp/ghs/subDetail.php?indexNum=617-021-00-1&subLang=ENmethylethylketone peroxide trimer.

In summary, we maintain our view that the physico-chemical and toxicological properties of the primary alkyl amines under question give rise to some concern regarding an aspiration hazard. On the other hand, the database is still considered somewhat inconclusive and thus we did not include this proposal in our report. Perhaps it could be worthwhile for RAC to have a discussion on the issue.

Appendix 3 – Rapporteur's with respect to Human Health endpoints.

Comments on Aspiration Hazard R65

The primary alkyl amines contain a long linear hydrocarbon moiety significantly influencing their physicochemical properties although for the presence of a nitrogen atom, are not hydrocarbons in the narrow sense. In the CLP Regulation Substances in Category 1 include but are not limited to certain hydrocarbons, turpentine and pine oil.

The kinematic viscosity of coco alkyl amines is 6.4 x mm^2/s at 60 °C. This value is below the threshold value of 20,5 mm2/s (at 40 °C): under this value a substance is classified in **Category 1** for **Aspiration Hazard R65-H304** according to point 3.10, table 3.10.1 of EU CLP Regulation 1272/2008 and according to DSD (kinematic viscosity for classification < 7 x mm^2/s at 40 °C).

It is to note that, although the kinematic viscosity for both CLP Regulation and DSD, is estimated at 40 °C, it is our opinion that the value calculated at 60 °C is very low and cannot exceed the threshold value for classification even if the measure were made at 40 °C.

Comments on Respiratory irritation R37

No human or specific animal data are available on respiratory tract irritation of the alkyl amines assessed in this report. It is noted that due to the low vapour pressure of the amine mixtures under investigation, exposure towards vapours is presumably low to negligible at room temperature. However, the situation might be different for scenarios in which exposure to aerosols can be anticipated.

- In an acute inhalation toxicity study with coco alkyl amines, irritation of the airways was observed along with slight histological changes at a concentration of only 0.099 mg test substance/L ambient air (cf. section **Error! Reference source not found.**).

As clear signs of respiratory irritation were observed the RAC supports the proposal to classify coco alkyl amines as **STOT SE 3**; **H335** (EU CLP Regulation) and **Xi**; **R37** (following the criteria of Annex VI to Dir. 67/548/EEC) **for respiratory irritation**: the same classification for (Z)-Octadec-9-enylamine (the other liquid amine) is warrented on the basis of read across approach..

Translation of R35 into Skin Corr 1A or 1B

From the two available studies on skin irritation/corrosion, it is concluded that coco alkyl amines should be classified as corrosive. C; R35 (following the criteria of Annex VI to Dir. 67/548/EEC) and Skin corr. 1A; H314 (EU CLP Regulation). (Hoechst AG, 1984 and Safepharm Laboratories Ltd., 1989)

The strict application of CLP criteria should on;y justify skin corrosion 1A due to the symptoms observation within 1 h after an exposure of 3 minutes.

In the Safepharm study no corrosive response was noted within one hour following the 3 minutes exposure. In the Hoechst study in only one of the three animals tested a score of 4 for erythema/eschar was noted already between 30 and 60 minutes after a 3 minute exposure, while scores from 1 to 2 were observed after 1 hour exposure. According to the CLP criteria category Skin corrosion 1B seems to be more appropriate.

Otherwise for tallow alkyl amines we support the classification R35- Skin corrosion 1B and For (Z)-octadec-9-enylamine we support the classification R34- Skin corrosion 1B