Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

tris(nonylphenyl) phosphite

ECHA/RAC/CLH-O-0000001402-87-01/A2

Adopted

26 October 2010

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: tris(nonylphenyl) phosphite
CAS number: 26523-78-4
EC number: 247-759-6

General comments

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
29/03/2010	**Germany / Nadja Prange / MSCA**	The German CA agree with the classification of TNPP as skin sensitizer. In TNPP, nonylphenol - a category 2 reproductive toxicant (CLP) - may be present as an impurity. The cut-off value for classification for category 2 reproductive toxicants such as nonylphenol is 3.0% (see table 3.7.2, CLP regulation). As stated in the CLH report TNPP may contain nonylphenol at concentrations that exceed the concentration limit of a reprotoxic ingredient of a mixture. As it is regulated in CLP regulation Art. 11 how substances are to be classified based on impurities it is unnessecary in our view to introduce an extra note.	Thank you for your support. We agree that article 11 with article 4(3) of CLP already give the obligation to add classification based on the impurity content if relevant and not part of the harmonised classification and an extra note in not necessary. Annex XV report has been modified accordingly.	Agreement noted Agreement noted, careful consideration nonylphenol either as impurity or as degradation product is the key issue for adequate TNPP classification

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01/04/2010	**Ireland / Health & Safety Authority / MSCA**	In the proposal for harmonised classification and labelling section of the Annex VI report (page 5), France have mentioned the possibility that a new note could be introduced to highlight to manufacturers & importers their responsibility to take account of the potential influence of impurities on the classification of the substance. The Irish CA does not feel that a new note is warranted in this case. Article 11(1) of CLP Regulation states that identified impurities "shall be taken into account for the purposes of classification, if the concentration of the identified impurity...is equal to or greater than the applicable cut-off value..." Therefore, we feel that the responsibility of manufacturers/importers to take account of the influence of impurities on the classification has already been covered by this Article.	We agree that article 11 with article 4(3) of CLP already give the obligation to add classification based on the impurity content if relevant and not part of the harmonised classification and an extra note in not necessary. Annex XV report has been modified accordingly.	Agreement noted
07/04/2010	**UK / Stephen Dungey / MSCA**	1) We recognise that most of the key studies have been reviewed and agreed under the Existing Substances Regulation (ESR), and this could be pointed out more clearly. In particular, if data have not been peer reviewed by Member States before, they should be highlighted in the main text. However, it has become clear from recent RAC discussions that information	1) This comment has been taken into account in the revised Annex XV report.	Noted and agreed. Extended and robust summary studies have been included and further developed/clarified for justification of the RAC opinion.

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		broadly equivalent to robust study summaries should be presented in the Annex XV (now VI) dossier if these are not included in the IUCLID file (ideally the robust study summaries should be provided). We therefore think additional details are required for some of the important studies (and these are mentioned in the specific comments below). 2) The dossier incorrectly refers to PBT criteria in places: this should be replaced by references to the DSD and CLP criteria. 3) Overall we can agree to the safety net classification of TNPP based on the effects observed in an acute Daphnia test with hydrolysis products, supported by the fact that toxicity was observed in a chronic sediment test with Lumbriculus. We presume that the effects are due to the formation of nonylphenol.	2) This comment has been taken into account in the revised Annex XV report (see section "4.3.3 Summary and discussion of bioaccumulation"). 3) We share your point of view and we agree on the safety net classification of TNPP based on the effects observed in an acute Daphnia test with hydrolysis products (see section "7.6 Conclusion on the environmental classification and labelling"). Concerning the chronic sediment test with Lumbriculus as no analytical follow-up was performed (neither for TNPP nor for its degradation product: nonylphenol) consequently, we "presume" that the effects are due to the formation of nonylphenol.	Agreement noted We agree with the changed classification as now proposed by the dossier submitter and as justified in the RAC opinion and Annex 1
08/04/2010	**Denmark / Peter Hammer / Danish EPA / National Authority**	At page 8. The text and table is a little misleading regarding the concentration limit for the content of nonylphenol. The concentration limit for additional	We agree that according to Directives 67/548/EEC and 99/45/EC, the concentration limit for Repr. Cat. 3; R62-63 is > 5 %. However, as NP	Noted. Potentially misleading information about suggested self classification due to different NP impurity contents is removed in Annex

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		classification applied for TNNP is >5% and not <5% according to 67/548/CEE. The additional classification applied for CLP is >3%. The classification Rep. cat. 3; R62/63 should be applied in the table under 67/548/CEE. At page 29, table 13. In the study by Tyl et al, 2002, the references for table 14 b and 14 c are wrong. The right references are table 13 b and c.	concentration is < 5 %, NP does not trigger reproductive classification of TNPP according to 67/548/EEC. Thank you for your comment. It has been modified in the Annex XV report.	1 to the RAC opinion. References corrected in Annex 1
08/04/2010	**Poland / MSCA**	France proposed to classify tris(nonylphenyl)phosphite as Xi; R43 (May cause sensitisation by skin contact) and R53 (May cause long-term adverse effects in the aquatic environment). According to the article 36.3 of regulation 1272/2008, where a substance fulfils for other hazard classes or differentiations than those referred to in art. 36.1 (CMR and respiratory sensitisation) and does not fall under art. 36.2 (active substances in plant protection products or in biocide products), a harmonized classification and labelling may also be added to Annex VI on a case-by-case basis, if justification is provided demonstrating the need for such action at Community level. We are not sure if it is a need to start a procedure for harmonisation of classification and labeling of tris(nonylphenyl)phosphite according to the article 36.3 of regulation No 1272/2008. We think that in section	The justification for submitting an harmonised classification proposal for TNPP is that it was on the 4th priority list under the Existing Substances Regulation and TNPP is therefore a transitional substance. In this context, full harmonisation was required. Conclusions were adopted for health endpoints by TC C&L but they could not be included in an ATP of Directive 67/548/EEC as the evaluation of TNPP was not finalised for environment. Now that environmental data are available, we consider it is necessary to establish an harmonised classification of TNPP as previously requested so as to finalise the work that has been done under the previous regulation.	We agree with the need for harmonised classification. Moreover, to the reasons explained by France, the substance would fulfil the criteria of the article 36(3), regarding the classification of substances fulfilling other hazard classes, such as R43 for human health and environmental hazard. It is true, that new environmental data is available (daphnia chronic study), but due to experimental shortcomings (in particular insufficient conditions for TNPP hydrolysis, and no analytical verification of nonylphenol concentrations), this study does not contribute to the justification for environmental classification.

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		"Justification that action is required on a community-wide basis" shall be added more information which demonstrate the need for a harmonized classification for that substance (for example, if there are information from poison centers that indicate that these substance or mixtures which contain these substance cause hazard to human health, such information should be included in this section). Now in these sections we can only read "TNPP was on the 4th priority list on the Existing Substances Regulation and it is therefore a requirement to harmonise classification for all endpoints justifying classification".		
		We believe that impurities of TNPP can have the potential influence on classification, but we can not agree with the statement that a new note could be created and added to the TNPP proposal to inform manufactures/importer as well as users that it can be necessary to complement the harmonized classification of TNPP. According to the general rules of classification of substances and mixtures (article 11 of regulation 1272/2008), if a substance contains another substance, itself classified as hazardous, whether in the form of an identified impurity, additive or individual constituent, this shall be taken into account for purposes of classification, if the concentration of the identified	We agree that article 11 with article 4(3) of CLP already give the obligation to add classification based on the impurity content if relevant and not part of the harmonised classification and an extra note in not necessary. The Annex XV report has been modified accordingly.	Noted. We also agree on the potential influence of impurities (esp. nonylphenol)

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		impurity, additive or individual constituent is equal or greater than, the applicable cut-off value. We have also some remarks to the information which can be found on the page number 4. On this page there are information on proposed classification based on Directive 67/548/EEC criteria and based on CLP criteria. There are also information on proposed labelling but only based on 67/548/EEC Directive. This page should also include information about proposed CLP labelling: signal word, hazard statements, pictograms. Editorial comments to the information on the page number 4: the statement "Proposed classification based on GHS criteria" should be change for "Proposed classification based on CLP criteria".	This comment has been taken into account in the revised Annex XV report (see section "Proposal for harmonised classification and labelling").	Noted.
08/04/2010	**Sweden / Swedish Chemicals Agency KemI / MSCA**	Nonylphenol, the main impurity of TNPP is already on CLP Annex VI. According to CLP Art. 11 if an impurity exeeds concentration above a cut-off value specified in section 1.1.2.2 of Annex I then it should be taken into account when classifying a substance. In general when the manufacturing process will always lead to production of a susbstance with a certain concentration of impurity then this should, in our opinion, be considered also in harmonised classification of the	We agree with previous MSCA comments that article 11 with article 4(3) of CLP already give the obligation to add classification based on the impurity content if relevant and not part of the harmonised classification and an extra note in not necessary. The Annex XV report has been modified accordingly.	Agreement noted, careful consideration of nonylphenol either as impurity or as degradation product is the key issue for adequate TNPP classification

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		substance. In this particular case, however, since the concentration of nonylphenol varies depending on a production process we believe that it would be difficult to arrive at one correct classification of TNPP that would reflect different concentrations of the impurity. Therefore we support France in their approach to classify TNPP, i.e.: (i) Classify TNPP without taking into account the main impurity. This will be done by industry who knows the concentration of nonylphenol in their TNPP (ii) To assign TNPP-entry in Annex VI an appropriate note explaining that impurities were not taken into account for the classification.		
08/04/2010	**UK / Andrea Caitens / MSCA**	Page 4 It should be made clear up front that the dossier is only proposing to harmonise the classification for skin sensitisation and long-term adverse effects in the aquatic environment and that all other data are provided for information only. It should also be made clear that no new data for the health endpoints are presented in the dossier, but it is based on the data already presented and agreed at TC C&L.	This comment has been taken into account in the revised Annex XV report. A sentence has been added on page 4 and in the introduction to section 5 to make this point clear.	Agreement noted Clarification noted
08/04/2010	**US / James Slosnerick / Dover Chemical Corporation / Company-Manufacturer**	Comments to the European Chemicals Agency on the Tris(Nonylphenyl) Phosphite (TNPP) (EC 247-759-6) Annex XV Report for Proposed Harmonised Classification and Labelling	Noted.	Noted

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		Dover Chemical Corporation appreciates the opportunity to submit these comments to the European Chemicals Agency (ECHA) on the December 2009 Annex XV Report from France for Proposed Harmonised Classification and Labelling of Tris(Nonylphenyl) Phosphite (TNPP) (EC 247-759-6). Dover Chemical Corporation, in conjunction with the TNPP Consortium, has been supportive of the work by France on the risk assessment of TNPP, including the development of new data used in the risk assessment and in this harmonised classification and labelling (C&L) proposal. Further, Dover Chemical Corporation is taking an active lead in developing the REACH registration materials for TNPP via its EU legal entity ICC Industries, B.V. These comments will focus on the two main items in the C&L proposal, namely the proposal to classify TNPP as a skin sensitiser and as toxic to the aquatic environment (ECHA: see the comments under section "Other hazards and endpoints").		

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08/04/2010	**Portugal / Maria do Carmo Palma / MSCA**	Considering the present proposal, we agree to establish an harmonised classification & labelling for TNPP. The proposed Classification and Labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive (health and environment).Therefore, we support the proposal.	Thank you for your support.	The support is noted

Carcinogenicity

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

Mutagenicity

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

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
08/04/2010	**Denmark / Peter Hammer / Danish EPA / National Authority**	Fertility and reproductive toxicity: Please, if possible to illustrate the paired epididymides relative weights with the statistical significance for the dose groups, as it is for the paired ovary weights (13b)?	It has been included in the revised Annex XV report.	Noted (now table 12b in Annex 1)

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		Please present the statistical significance for the decrease in litter size on pnd 0 observed at 1000 mg/kg/day in table 13C.	It has been included in the revised Annex XV report.	Noted (now table 12c in Annex 1)
		Regarding the decreased paired epididymides weight, the difference in the dosing period could be a reasonable explanation for, why this organ weight is decreased in the F1 males and not in the F0 males. The F1 males are dosed during the critical period of reproductive system development thereby enhancing sensitivity to endocrine disrupters compared to the parent generation, which are only dosed during adulthood. Therefore DK does not agree with rapporteur that this result is of un-certain toxicological significance. A decrease in epididymis weight is also rapported in at least two rat studies with gestational exposure to nonylphenol (Hossaini et al., 2001 ; Han et al., 2004). Developmental toxicity:	We agree with this comment. However, in the absence of accompanying histological effect on the epididymes and in the absence of changes in any of the other andrology parameters measured, it is not considered that this effect is relevant for classification purpose.	RAC has agreed to not further scrutinise the information on reproductive toxicity provided by the dossier submitter just for information purposes. Since final conclusions for health endpoints of the Technical Committee on Classification and Labelling of the European Chemicals Bureau (ECB TC C&L) in 2005, neither the dossier submitter nor the public consultation revealed new information on reproductive toxicity of TNPP to be considered and prepared for the processed CLH proposal This is clearly stated and justified in the RAC opinion and its Annex 1 (intro to section 5.8).
		Based on the study by Tyl et al., 2002 it is not appropriate risk assessment to use the culled pups on pnd 4 to derive a NOAEL for teratogenicity for several reasons: 1) In this study, the litter size is 10, while it is 20 in a proper teratogenicity study. 2) Generally, in a teratogenicity study all foetuses in a litter are investigated, while	Noted. However, the aim of the dossier is not to discuss risk assessment and not to establish NOAEL. Besides, NOAEL provided in this report were discussed and validated in the context of the European Risk Assessment Report and no further discussion on this point is considered relevant in the present context (EU RAR	Noted. RAC has agreed to not re-open earlier discussions formally concluded by other EU-bodies, unless new information has been provided.

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		in this study by Tyl et al. only looked for malformations in the culled pups. As a consequence of the decreased litter size in the high dose group, only around 2 pups/litter can be used to investigate malformations in the high dose group while around 4 pups per litter is used in the other groups. 3) It should be kept in mind that dams often eat the pups, which are unable to survive including pups with malformations. Hence, pups with severe malformations are either dead or eaten by the dam before culling at pnd 4 and therefore not investigated. Consequently, it is most inappropriate to conclude that NOAELterato is > 1000 mg based on these investigations. Therefore NOAELterato should not be used in the risk characterisation. However, based on a relatively small number of investigated pnd 4 pups, it can be concluded that no signs of developmental toxicity was observed.	2002a).	

Respiratory sensitisation

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Other hazard classes

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29/03/2010	**Germany / Nadja Prange / MSCA**	Page 36, Table 8: Acute toxicity to aquatic invertebrates Test #1: Toxicity value (EC50 (48h) = 0.009 mg/L) was just based on NP. In our opinion it should be based on the whole TNPP hydrolysis products. Which would mean an EC50 (48h) of 0.3 mg/L. This value is also supported by Test #2. Test #1 shows definitely the presence of toxic effects to Daphnia, if TNPP is used as parent compound. Using this toxicity value for classification it would also change the classification into N, R50 – 53 (67/548/EEC) or according to CLP regulation as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410).	We share your point of view and we agree to the safety net classification of TNPP based on the effects observed in an acute Daphnia test with hydrolysis products (see our new proposition of classification in section "7.6 Conclusion on the environmental classification and labelling").	We agree with the changed classification as now proposed by the dossier submitter and as justified in the RAC opinion and Annex 1.
01/04/2010	**Ireland / Health & Safety Authority / MSCA**	Skin Sensitisation: The Irish competent authority agrees with the proposed classification Xi: R43 (Directive 67/548/EEC) and Skin Sens 1 H317 (EC No. 1272/2008) based on the justification provided. Environmental Fate properties: In relation to paragraph two of section 4.1.3, the Irish competent authority would like to express concern for the disparity between the statement "nonylphenol…being readily biodegradeable" and the information provided in the risk assessment report for	Thank you for your support. We agree with you and we have corrected it in the Annex XV report (see section "4.1.3 Summary and discussion of persistence").	Support noted The agreement has been noted. The reference (EC, 2002) has been included in section 4.1.3.

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		nonylphenol (EU RAR, 2002b) which states from • section 3.1.1.2.2: "In both the OECD 301B and 301F tests, nonylphenol shows significant biodegradation but fails to meet the criteria for ready biodegradability (10 day window) and so these results will be take to give an indication of inherent biodegradability rather than ready biodegradability.", and also • EU RAR Section 3.1.1.2.4: "The data available indicate that nonylphenol undergoes biodegradation in water, sediment and soil systems. The results from standard biodegradation tests are variable but indicate that nonylphenol is probably inherently biodegradable." and "Based upon the data nonylphenol is not considered readily biodegradable. However, significant biodegradation was seen in ready biodegradability tests when adapted micro-organisms were used. The widespread use and distribution of nonylphenol and its ethoxylates makes some degree of acclimation more likely. Therefore nonylphenol is considered as being inherently biodegradable and a rate constant of 0.1 h-1 will be used in the sewage treatment model." We feel that the statement provided in the Annex VI report is incorrect due to the		

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		evidence provided in the EU risk assessment report for nonylphenol.		
01/04/2010	**Ireland / Health & Safety Authority / MSCA**	(This supercedes the previous submitted comment for the Environment endpoint only) The Irish competent authority agrees with the proposed classification R53 (Directive 67/548/EEC) and Aquatic Chronic 4 – H413 (EC No. 1272/2008) based on the justification provided. The Irish competent authority has the following comment: In relation to paragraph two of section 4.1.3, the Irish competent authority would like to express concern for the disparity between the statement "nonylphenol…being readily biodegradeable" and the information provided in the risk assessment report for nonylphenol (EU RAR, 2002b) which states from • section 3.1.1.2.2: "In both the OECD 301B and 301F tests, nonylphenol shows significant biodegradation but fails to meet the criteria for ready biodegradability (10 day window) and so these results will be take to give an indication of inherent biodegradability rather than ready biodegradability.", and also• EU RAR Section 3.1.1.2.4: "The data available indicate that nonylphenol undergoes biodegradation in water, sediment and soil systems. The results from standard biodegradation tests are variable but indicate that nonylphenol is	See our new proposition of classification in section "7.6 Conclusion on the environmental classification and labelling". We agree with your comment on nonylphenol, we have corrected it in the Annex XV report (see section "4.1.3 Summary and discussion of persistence").	We agree with the changed classification as now proposed by the dossier submitter and as justified in the RAC opinion and Annex 1. We agree with MS comments and the need of clarification regarding nonylphenol degradability. It has been accounted.

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		probably inherently biodegradable." and "Based upon the data nonylphenol is not considered readily biodegradable. However, significant biodegradation was seen in ready biodegradability tests when adapted micro-organisms were used. The widespread use and distribution of nonylphenol and its ethoxylates makes some degree of acclimation more likely. Therefore nonylphenol is considered as being inherently biodegradable and a rate constant of 0.1 h-1 will be used in the sewage treatment model." We feel that the statement provided in the Annex VI report is incorrect due to the evidence provided in the EU risk assessment report for nonylphenol.		
07/04/2010	**UK / Stephen Dungey / MSCA**	Table 1 (p. 13): There is no discussion of the reliability of the water solubility predicted by QSAR – it should be clarified whether the substance and prediction are within the model domain. The information in Appendix II suggests that a new water solubility result is available – this should be provided if so. The measured log Kow value of 14 is well outside the limit of the method (0 to 6), and its reliability is unclear. We suggest it is expressed as '>10'.	See section "1.3 Physico-chemical properties". The water solubility predicted by QSAR should be interpreted with care, as it was based on a highly uncertain log Kow value, and is presumably outside the model domain. Actually, no new water solubility result is available. The Commission Regulation (EC) No 466/2008 specified that a new test was required but it was not specified in the minutes of the last TC NES. In addition, the TC NES agreed with the water solubility's range currently used in the RAR. Consequently, the industry considered that this information remains filled to date.	The TNO detection limit of 0.05 mg/L is noted in the 2008 draft RAR (EC, 2009 in reference list of Annex 1) as a personal communication. The dossier submitter confirmed this information as oral statement without any written reference. Regarding the model domain the Episuite (WSKOWWIN) estimates water solubility based on Log Kow and correction factors. The range of water solubility varies form a few ppb to miscible. We agree with the MS comment, and

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			We agree with your comment and we proposed to express the log Kow as "> 10" in the Annex XV report although the TC NES agreed with a log Kow value of 14.	the suggestion of express the log Kow as ">10", since the HPLC method (OCDE 117) covers log Pow in the range of 0 to 6. So the result is out of the limit of the method. Anyway, it is indicated that the log Kow of 14 was used for calculating table 4 values.
		Section 4.1.1 (p. 15): Hydrolysis is a key property for this proposal. Further details should be provided regarding the test method and conditions for the key study, and the result should be expressed as a half-life if possible. Further information on hydrolysis is presented in the ESR Risk Assessment Report (RAR) and referred to in Appendix II, and this should be included in the discussion in the main text. In addition, it seems clear that despite the high hydrophobicity, the substance does produce nonylphenol in water (0.3 mg/l of nonylphenol was formed after leaving TNPP in water (loading rate not given) for 78 hours at room temperature according to the Hydroqual Labs (2001a) acute Daphnia test reported in Table 8 (p. 36)). Similarly, the summary of the Hydroqual Labs (2001b) algal test in Table 10 (p. 37) suggests that hydrolysis was occurring. This information should also be mentioned in this section to provide further context for the possibility and relevance of nonylphenol formation (since this would seem to be the main reason to classify).	This comment has been taken into account in the revised Annex XV report (see section "4.1 Degradation").	Agree with MS regarding hydrolysis and the relevance of nonylphenol formation. See more explanation in Annex 1. Besides clarifying amendments in table 2, a concluding paragraph is added to section 4.1.1

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		Section 4.1.2.3 (p. 16): The OECD 301B test summarised in Table 3 should provide additional details, such as the source of the inoculum and adaptation method.	This comment has been taken into account in the revised Annex XV report (see section "4.1.2.2 Screening tests").	Agree and noted
		Section 4.1.3 (p. 16): The opening paragraph refers to atmospheric half-life from a QSAR model, although this is not relevant to the proposal (the reliability of the prediction is unknown, but the very low vapour pressure could be referred to if it is retained). The reference to ozone depletion is unnecessary – e.g. there are no halogen atoms in the structure.	We deleted this part.	Agree and noted
		The rate of hydrolysis should be mentioned. The discussion of the nonylphenol degradation product is a little confusing – it is said to be readily biodegradable at first but only inherently biodegradable later on. Would the rate of formation of nonylphenol from TNPP be less than the rate of removal of NP once formed?	These comments have been taken into account in the revised Annex XV report; we corrected information on nonylphenol (see section "4.1.3 Summary and discussion of persistence").	Agree and noted, section 4.1.3 has been amended for further clarification.
		The final paragraph refers to the PBT criteria – this should be replaced by the classification criteria instead.	We agree with you and we have corrected it in the Annex XV report (see section "4.1.3 Summary and discussion of persistence").	Agree and noted
		Section 4.2.1 (p. 17): The predicted adsorption coefficients are based on a highly uncertain log Kow value, and are	We agree with you, we mentioned it in section "4.2.1 Adsorption/desorption".	Agree and noted

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		presumably outside the domain of the models. This could be briefly mentioned.		
		Section 4.2.2 (p. 17): Given the large uncertainty in the water solubility values, we wonder whether the numerical values for the Henry's Law constant are helpful. They suggest significant volatilisation from water is possible, but this is likely to be misleading.	We agree with you, we mentioned the uncertainty of the Henry's Law constant value (see section "4.2.2 Volatilisation").	Agree and noted
		Section 4.3 (p. 18-20): Please mention the basis for the BCFWIN prediction (log Kow?). We do not see any need to mention BCF data for nonylphenol here.	The BCF was based on a log Kow of 20.05 (estimated) (see section "4.3.1.1 Bioaccumulation estimation").	Agree and noted
		The validity of the earthworm BCF prediction is unclear and conflicts with the assumption of low accumulation given in the summary; since it is not relevant for the classification criteria we suggest it is deleted.	We agree with you and we deleted the BCF data for nonylphenol and the earthworm BCF prediction.	Agree and noted
		The Environment Agency has published a report on molecular size estimation using computer programmes, and there is some variability since different models provide different dimensions (see http://publications.environment-agency.gov.uk/pdf/SCHO0109BPGT-E-E.pdf). Some further description of the	Thank you for this information.	This information has been included. Available information remains insufficient for unequivocal conclusion on bioaccumulation.

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		molecular size model used by CERI is therefore needed. In addition, the dimensions of Opperhuizen et al. (1985) are not reliable (see the Environment Agency report). We note that there is a reference in Appendix II to a calculation using the OASIS model – has this been done yet?	The OASIS model prediction: this information remains unfilled to date.	Noted.
		The reference to the PBT criteria at the end of the summary should be replaced by the classification criteria, and a conclusion on the BCF for comparison with the criteria should be provided.	This comment has been taken into account in the revised Annex XV report (see section "4.3.3 Summary and discussion of bioaccumulation").	Agree and noted
		Section 7 (p. 34): Please mention the analytical limit of detection. Given the physico-chemical properties of the substance it would be useful to mention the exposure conditions of the tests – e.g. were they static? We suggest adding more details about the studies to the main text, as presented in the ESR RAR. The fish and algal results should be expressed as showing no effects up to the limit of water solubility.	This comment has been taken into account in the revised Annex XV report (see section "7.1 Aquatic compartment (including sediment)").	Agree, further amendments for clarification in Annex 1
		Table 8 (p. 36): The presentation of the Hydroqual Labs (2001a) results is not very clear – it is apparently based on total mass of initially added TNPP, but this is not mentioned in the paragraph above (the ESR RAR text is clearer). Also, it is not clear why the Ciba-Geigy study is	This comment has been taken into account in the revised Annex XV report (see section "7.1.1.2 Aquatic invertebrates").	Agree, further amendments for clarification in Annex 1

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		considered invalid – please explain (as in the ESR RAR).		
		Table 9 (p. 37): We realise that the chronic Daphnia study has not been discussed by the Member States before, and is not relevant for classification at the moment. However, some further details would be helpful since the result is used in the summary as a surrogate acute test. How was the test solution prepared, and what were the exposure conditions? Although no effects were observed, could this be due to the low loading rate or the possible lack of substance in the water (e.g. due to adsorption)?	For more details about the chronic Daphnia study see section "7.1.1.2 Aquatic invertebrates".	Agree, further amendments for clarification in Annex 1
		Section 7.1.1.4 (p. 38): The Lumbriculus test is interesting because it appears to demonstrate toxicity, although it is disappointing that no analytical monitoring was performed for degradation products. For completeness, it might help to add information on the organic carbon content of the sediment and whether the results are expressed in dry or wet weight.	We added information in the revised Annex XV report see section "7.1.1.4 Sediment organisms".	Agree, further amendments for clarification in Annex 1; validity status changed to 2 because of missing analytics.
		Section 7.4.1 (p. 39): The micro-organism tests are not used in classification. For the first one, the IC50 of 16 mg/l presumably relates to the reference substance?	Yes, the IC50 of 16 mg/L relates to the reference substance. We mentioned it in the Annex XV report (see section "7.4.1 Toxicity to aquatic micro-organisms").	Noted
		Section 7.6 (p. 40-41): We think this section should be presented slightly	See our new proposition of classification in section "7.6 Conclusion on the	See amended conclusions section as justification for the RAC opinion

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		differently: 1. The first issue is whether there are any toxic effects in acute tests with TNPP up to its water solubility limit. There do not seem to be. 2. The second is whether R53/Aquatic Chronic 4 is appropriate based on its intrinsic persistence and bioaccumulation potential. The current bioaccumulation conclusion as written in Section 4.3 is unclear in this respect. As there appear to be valid chronic data for invertebrates and algae, the NOEC escape clause should be considered. 3. Finally, there is the issue of possible hydrolysis to nonylphenol. The text in this section is slightly confusing on this point, stating "nonylphenol is likely to be the toxic agent present in the test solutions……. no explanation can be found [for] the toxicity observed during this short-term toxicity testing with daphnids". The section also downplays the acute toxicity test on Daphnia with hydrolysis products, saying "the test results present some uncertainties so it was not taken into account for the classification of TNPP." This does not seem to fit in with the final conclusion. Overall we can agree to the safety net classification of TNPP based on the effects observed in the acute Daphnia test with hydrolysis products, supported by the fact	environmental classification and labelling".	supporting the dossier submitter's changed classification proposal.

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		that toxicity was observed in a chronic sediment test with Lumbriculus. We presume that the effects are due to the formation of nonylphenol. Editorial comments		
		Section 1.2 (p. 7-8, & 10): The structural diagrams imply that the alkyl chains are linear. This is not the case according to our understanding of the starting material, and the diagrams should either be redrawn with branches or a footnote added.	This comment has been taken into account in the revised Annex XV report (see section "1.2 Composition of the substance").	Agree, minor editorial amendments
		Section 1.2 (p. 8-9): We think it might be simpler to acknowledge the fact that commercial TNPP may contain a classified impurity and that suppliers will need to classify accordingly, rather than present the classification tables in this section.	So as to be comprehensive in the information provided, we prefer to maintain this information in the report.	We agree with submitter's response after corresponding clarifications in the resubmitted dossier, it can be considered as additional information.
		Table 3 (p. 16): The studies that are summarised in this table are screening rather than simulation tests, so ideally this table should be moved to Section 4.1.2.2 and renamed.	We agree with you and we have corrected it in the revised Annex XV report (see section "4.1.2.2 Screening tests").	Agree and noted.
		Section 4.2.3 (p. 17): Information on behaviour in an STP is not needed for the proposal.	We deleted this part.	Agree and noted
		Section 4.3 (p. 18-20): Reference to the PBT subgroup should be replaced by the	We have corrected it.	Agree and noted

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		REACH TGD. Section 4.4 (p.20): This section is not relevant to classification so the text should be deleted. Section 7.1.1.3 (p. 37): The species Selenastrum capricornutum is now Pseudokirchneriella subcapitata.	 We deleted this section in the revised Annex XV report. We have corrected it.	 Agreed and noted Agreed and noted
08/04/2010	**Denmark / Peter Hammer / Danish EPA / National Authority**	Environmental propoerties: Impurities, nonylphenol, high purity TNPP with 0.1 % nonylphenol, table at the end of the section: The rules for setting specific concentration limits under CLP are analogous to the rules under 67/548, and give the same result given that the substance is classified Chronic 1/R50-53. So the classification of the "mixture" due to this impurity would be Chronic 3/R52-53. The fish acute toxicity test 3, 48 h LC50 for Leuciscus idus: If no physical effects have been ob-served, and if a dose – response relationship has in fact been observed, the LC50 can be set equal to the water solubility level. Classification and labelling: DK suggests that classification of tris(nonylphenyl) phosphite as a	 We agree with you and we have corrected it in the revised Annex XV report (see section "1.2 Composition of the substance"). In fact, lethal effects were observed at 10 mg/L (LC100 (48h) = 10 mg/L and LC0 (48h) <5.8 mg/L). Consequently, based on a dose-response relationship an LC50 was estimated at 7.1 mg/L. Three dams at the highest limit dose of 1000 mg/kg died on GD 22 and were in	 Noted. RAC opinion + Annex 1 clarify that classification related to impurities is not part of the proposal for harmonised classification. Based on the available information and its considerable uncertainties, RAC concludes to recommend no harmonised M-Factor for TNPP. Noted, test however not valid due to lack of analytical monitoring, unspecified grade of tested TNPP, etc. RAC has agreed to not further scrutinise the information on reproductive toxicity

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		reproductive toxicant, cat 3 should be applied, while it should be taken into account, that the dystocia observed in the high dose dams apparently couldn't be explained by a general toxicity of these dams, but rather be explained in a specific hormone-related effect causing dystocia. It should be noticed that scientific papers have suggested that other endocrine-disturbing mecha-nism than the oestrogenic activity can be involved in the reproductive toxicity of nonylphenol. A re-view of this literature would be appropriate to include in this Annex XV report. Proposed classification: (67/548/CEE): Xn -Rep. cat 3; R62. Xi - R43. N - R53. (CLP): Repr- 2; H361f Skin Sens. 1 – H317 Aquatic Chrnic 4 – H413 Kind regards Henning Ian Clausen / Peter Hammer Sørensen	the midst of delivery. These observations are consistent with dystocia. However, considering that during late gestation lack of daily adjustment of the dosing volume may have resulted in overdosing, excessive toxicity is likely in these dams. Such effect was not reproduced at lower dose in this study as well as in a multiple-generation study in diet. It is therefore not considered to justify classification. Studies that were considered as valid in the EU RAR are available on TNPP and review of mechanistic information of nonylphenol is not relevant in this context. A potential classification for reproductive toxicity was previously discussed at TC C&L. No classification was finally concluded and no new relevant data on TNPP is available has been identified since this recommendation (see summary records in appendix I of the Annex XV report).	provided by the dossier submitter just for information purposes. Since final conclusions for health endpoints of the Technical Committee on Classification and Labelling of the European Chemicals Bureau (ECB TC C&L) in 2005, neither the dossier submitter nor the public consultation revealed new information on reproductive toxicity of TNPP to be considered and prepared for the processed CLH proposal This is clearly stated and justified in the RAC opinion and its Annex 1 (intro to section 5.8). RAC has indeed agreed to not re-open earlier discussions formally concluded by other EU-bodies, unless new information has been provided.

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08/04/2010	**Sweden / Swedish Chemicals Agency KemI / MSCA**	Health: We agree with the proposed classification. Environment: In case of TNPP nonylphenol is not only an impurity but also a degradation product (i.e. hydrolysis product) and therefore its contribution to the overall toxicity should be taken into account. The majority of the aquatic toxicity tests were done on a high purity of TNPP, which implies that the toxicity of nonylphenol–the degradation product formed during the test, should have also been taken into account. There is a lack of reliable acute toxicity tests that were performed on TNPP. Due to its low water solubility (< 0.05 mg/L) the substance was tested with WAF method or even above its water solubility. Therefore these results are difficult to interpret. Although there are reasons to believe that TNPP would not cause acute effects, long-term effects cannot be excluded. This is mainly based on the fact that TNPP degrades to nonylphenol in a slow process of hydrolysis (0.1% after 10 days). As shown in the test on Daphnia sp. that was done on hydrolysis products of TNPP obtained after leaving TNPP for 78h at room temperature, the amount of nonylphenol formed might have caused toxic effects measured in the test. Taking into account that the substance is not readily biodegradable and its	Thank you for your support See our new proposition of classification in section "7.6 Conclusion on the environmental classification and labelling".	Support noted See amended conclusions section as justification for the RAC opinion supporting the dossier submitter's changed classification proposal.

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		bioaccumulation potential cannot be excluded (lack of measured BCF, Log Kow of 14 that could imply low bioaccumulation), we agree with the submitting MSCA that R53 /Chronic IV 413 is justified. Detailed comments: p.9 please correct the table. The corresponding classification of R52-53 in CLP is Chronic 3 H412. 4.1.3. Please clarify the statement on biodegradation of nonylphenol. If susbstance is considered to be inherently degradable it does not mean that it is readily biodegradable.	We agree with you and we have corrected it in the revised Annex XV report (see section "1.2 Composition of the substance" and "4.1.3 Summary and discussion of persistence").	Noted
08/04/2010	**US / James Slosnerick / Dover Chemical Corporation / Company-Manufacturer**	I. Comments on the Proposed Skin Sensitisation Classification There are two OECD 406 guideline studies for TNPP in guinea pigs, a 1992 guinea pig maximization test (GPMT) (Ciba-Geigy 1992) that showed signs of sensitisation and a 2001 Buehler method study (Tay 2001) that did not show a response. Based on these studies, the Annex XV Harmonised C&L proposes a classification of Xi, R43 based on Directive 67/548/EEC and Skin Sensitiser 1, H317 based on the Classification, Labelling and Packaging (CLP) regulation. There is no further discussion about the relative strengths and weaknesses of these data in the Annex XV C&L document; however, the human	We agree that LLNA is the preferred method for detection skin sensitisation under REACH. However, the GPMT and Buehler test are also considered relevant for hazard identification. Besides, the positive result obtained in the GPMT is clearly in agreement with the guidance on application of CLP classification criteria for skin sensitisation (http://guidance.echa.europa.eu/docs/guidance_document/clp_en.pdf), that states in section 3.4.2.3.4 that " a substance may be classified a skin sensitiser on the basis of a positive test result in one of the above described animals [LLNA, GPMT and Buehler]".	Disagreement with proposed classification has been noted by RAC co/rapporteurs. RAC supports classification proposal of dossier submitter and confirms accordance to classification criteria. Justification has been amended by further information.

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		health portion of the draft TNPP risk assessment (EU RAR 2007) offers the following rationale for the classification of TNPP as a skin sensitiser: "Adjuvant-type tests are likely to be more accurate in predicting a probable skin sensitising effect of a substance in humans than those methods not employing Freunds Complete Adjuvant (FCA), and are thus the preferred methods. Then, the results of the Guinea-Pig Maximisation test will be used for the risk assessment, as this test is considered to be more sensitive than the Buehler test." While the proposed classification may be technically consistent with the results of the GPMT study, Dover Chemical Corporation does not believe that the maximisation method or that the use of adjuvant-type tests are more "accurate" or "preferred" methods to assess sensitisation. In fact, it is well established that the GPMT can provide false positive results and, as such, these results should be considered critically given the recent reviews and guidance that have been developed on this endpoint by ECETOC (ECETOC 1999, 2000, 2003), ECHA (2008), and Steiling (2001). For example, ECHA concluded in the REACH endpoint guidance (Section R.7.3.7.1; ECHA 2008) that: "The use of adjuvant in the GPMT may lower the threshold for irritation and so	Considering the level of impurities, none of the impurities or additives of TNPP are known to have skin sensitising effects and the possibility that the positive response observed in the GPMT is due to its impurities is therefore unlikely. Besides, classification for skin sensitisation was previously discussed at TC C&L. Classification Xi; R43 was finally concluded based on the two tests that are discussed here and their in-depth discussion in the context of the EU RAR. No new relevant data on TNPP is available has been identified since this recommendation (see summary records in appendix I of the Annex XV report).	RAC has indeed agreed to not re-open earlier discussions formally concluded by other EU-bodies, unless new information has been provided.

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		lead to false positive reactions, which can therefore complicate interpretation…" Given the "very slight to moderate" skin irritation potential of TNPP (conclusion from the EU RAR 2007), the mild to moderate responses in the GPMT study, and the negative Buehler study using neat TNPP, it appears likely that the GMPT study of TNPP produced false positive reactions. Also, the current preferred method for skin sensitisation under REACH and CLP is not the GPMT as the risk assessment states, but the Murine Local Lymph Node Assay (LLNA). ECHA notes that the LLNA "has been shown to have clear animal welfare benefits and scientific advantages compared with the guinea pig tests," such as the GPMT. Dover Chemical Corporation is willing to discuss with ECHA/France whether the conduction of an LLNA study on TNPP might be useful to help further elucidate this endpoint. Regardless, it is clearly incorrect for the Annex XV C&L proposal to accept the results of the GPMT study over that of the Buehler study simply based on the position that the GPMT and the use of an adjuvant is "more accurate" and "preferred." There are additional aspects to consider in evaluating these two studies, including the fact that the test substance in the Tay (2001) Buehler study is of much higher purity (99.3%) than that of the Ciba-Geigy		

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		(1992) GMPT study (>94%) and the fact that the impurities are not described in Ciba-Geigy study. In summary, it is not appropriate to base the classification on the single positive GPMT study result and ignore more recent data developed on a higher purity TNPP test material, especially since potential concerns that have been identified with the GMPT test method. Considering that the Buehler study (Tay 2001) was conducted using neat TNPP (>99% pure) and observed no signs of sensitisation, these results should guide the classification decision. II. Comments on the Proposed Chronic Aquatic Toxicity Classification The Annex XV Harmonised C&L assessment proposes a classification of R53 based on Directive 67/548/EEC and Aquatic Chronic 4, H413 based on CLP. The rationale for this classification is not based on the result of TNPP aquatic studies, which the assessment concludes: "TNPP may not cause short and long-term adverse effects in the aquatic environment…" "Available valid acute studies performed on TNPP… does not support a classification for short-term toxicity." Rather, the proposed classification is based on the fact that one potential degradation chemical of TNPP is nonylphenol (NP),	See our new proposition of classification in section "7.6 Conclusion on the environmental classification and labelling". We would like to point out that although TNPP hydrolysis in the aquatic compartment will not be considered as an important degradation phenomenon, it should be taken into account that during the processing of polymers using TNPP as antioxidant, TNPP will undergo hydrolysis, resulting in the release of nonylphenol in the environment. Therefore, the hydrolysis of TNPP leading to the formation of NP during processing (which is classified for its	Disagreement with proposed

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		which itself is classified as N; R50-53 under Annex I to Directive 67/548/EEC. However, the C&L proposal appears to ignore the data on TNPP degradation presented in the draft risk assessment (EU RAR 2008), which shows that TNPP has been shown to be stable in water; nor does it consider the conclusion of the RAR that: "hydrolysis of TNPP in the aquatic environment will not be considered an important phenomenon." The RAR goes on to further state that: "This is based on the expected very low water solubility of the substance that would not enable hydrolysis to occur in large amount." Based on the conclusions that TNPP is not toxic to aquatic organisms and that hydrolysis is not considered an important phenomenon, it appears inappropriate and unjustified to classify TNPP as R53. The recently conducted OECD guideline chronic daphnia study (Sayers 2009) showed no chronic aquatic effects at loading levels above the maximum water solubility limit and even included the use of co-solvent (acetone) in order to facilitate the solubility of TNPP in the test system. The C&L proposal discusses the fact that TNPP is extremely poorly water-soluble, is not readily biodegradable and has log Kow $\geq$ 3. While none of these facts are in question, they are not more relevant than the actual chronic aquatic toxicity testing	toxicity for the aquatic environment) was considered in the risk assessment and has to be considered for its environmental classification.	classification has been noted by RAC co/rapporteurs. See amended conclusions section and amendments in Annex 1 as justification for the RAC opinion supporting the dossier submitter's changed classification proposal.

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		data for TNPP. The lack of chronic effects by TNPP simply does not support a classification of R53. III. References Ciba-Geigy, (1992). Skin sensitisation test in the Guinea pig, Maximisation test. Test number 924058. ECETOC (1999) Technical Report 78 - Skin Sensitisation Testing: Methodological Considerations. (August 1999). ECETOC (2000) Monograph 29 - Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment. (September 2000). ECTOC (2003) Technical Report 87 - Contact Sensitisation: Classification According to Potency. (April 2003). ECHA (2008). Guidance on information requirements and chemical safety assessment: Chapter R.7a: Endpoint specific guidance. (May 2008). EU RAR (2007). Tris Nonylphenol Phophite: Risk Assessment Report: Human Health Assessment. France. Draft of February 2007. EU RAR (2008). Tris Nonylphenol Phophite: Risk Assessment Report: Environmental Risk Assessment. France. Draft of October 2008. Sayers L.E. (2009). TNPP (Trisnonylphenyl Phosphite) - Full Life-Cycle Toxicity Test with Water Fleas, Daphnia magna, Under Static-Renewal		

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		Conditions, Following OECD Guideline #211. Wareham, MA, Springborn Smithers Laboratories. Steiling W, Basketter DA, Berthold K, Butler M, Garrigue J-L, Kimber I, Lea L, Newsome C, Roggeband R, Stropp G, Waterman S, Wieman C. (2001). Skin sensitisation testing – new perspectives and recommendations. Food and Chemical Toxicology 39: 293-301. Tay CH, 2001d. Tris-nonylphenol (TNPP): Buehler sensitisation test - (OECD 406). Unpublished Report n° 01-4176-G4, Toxicon Corporation. (ECHA: transferred from general comments)		