Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

1,4-dimethylnaphthalene

EC Number: 209-335-9
CAS Number: 571-58-4

CLH-O-0000006734-69-01/F

Adopted

5 December 2019

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 1,4-dimethylnaphthalene
EC number: 209-335-9
CAS number: 571-58-4
Dossier submitter: The Netherlands

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.05.2019	Germany		MemberState	1

Comment received

We acknowledge the discussion of toxicological information on other naphthalene compounds. We kindly ask the dossier submitter for a more detailed discussion of the following aspects:
1. Naphthalene is classified as carcinogen Category 2. In contrast to naphthalene no nasal tumours were observed in rats after exposure to 1,4-dimethylnaphthalene. Therefore, the toxicological profile seems different for 1,4-dimethylnaphthalene. This should be discussed in the dossier.
2. Regarding the species difference in lung susceptibility we would appreciate if the dossier submitter could deliver information why the metabolite 1R, 2S-naphthalene oxide seems to be more relevant for formation of lung tumours than the metabolite 1S, 2R-naphthalene oxide.
3. Furthermore we kindly ask the dossier submitter to explain the relevance of pulmonary alveolar proteinosis on formation of lung tumours.

Dossier Submitter's Response

Thank you for your comment. Each individual comment is addressed below.

1) Except for the acute inhalation study all studies conducted with 1,4-DMN were carried out via the oral route while nearly all studies with naphthalene were carried by inhalation exposure. This makes it difficult to compare the toxicity profile of the two substances. The nasal tumors with naphthalene were observed in a study in which rats were exposed by inhalation while the rat carcinogenicity study with 1,4-DMN was carried out via the oral route. For the classification and labelling proposal we focussed on the available studies with 1,4-DMN itself.

2) As far as we are aware the exact reason on why 1R,2S-naphthalene oxide seems to be more relevant for formation of lung tumors is not fully known. The 1R,2S-epoxide has

been shown to be metabolized to the dihydoriol at a much faster rate than the 1S,2R epoxide and it has been postulated that this may contribute to the difference in toxicity between the two enantiomers[1].

3) Alveolar proteinosis has been linked to increased pneumocytic proliferative activity and hereby the likelihood of tumor formation although it has also been postulated that pulmonary alveolar proteinosis may develop coincidentaly with lung cancer[2].

References

[1] Bailey et al. 2016 Hypothesis-based weight-of-evidence evaluation and risk assessment for naphthalene carcinogenesis. Crit. Rev. Toxicol 2016:46(1):1-42

[2] Friemann et al. 1994 Pulmonary alveolar proteinosis in rats after administration of quartz: its possible role in morphogenesis of lung cancer. Journal of Cancer Research and clinical oncology 1994: 120(6): 348-353

RAC's response

Thank you for your comments and responses.

1) RAC agrees with the DS that it is difficult to compare the toxicity of naphthalene and 1,4-dimethylnaphthalene (1,4-DMN). Differences in toxicokinetics exist between the two compounds. Therefore, RAC agrees to classify the substance on the basis of available data on 1,4-DMN only.

2) Noted.

3) Based of the results observed in the carcinogenicity study available in mice with 1-MN and 2-MN, no clear relation between alveolar proteinosis and tumour was observed. Indeed, alveolar proteinosis was observed in both males and females and lung adenoma was only increased in males.

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	France		MemberState	2

Comment received

FR: 10.9.2 Comparison with the CLP criteria page 31
Based on the data reported:
- specific data with 1,4-dimethylnaphthalene (carcinogenicity in rats)
- read-cross from carcinogenicity studies in mice with 1-methylnaphthalene and 2-methylnaphthalene
- species comparative metabolism
The conclusion form DS could be supported for oral route.
However, no data has been reported for inhalation while 1,4-dimethylnaphthalene is a volatile substance and carcinogenicity studies by inhalation performed with naphthalene are available (NTP studies in rats and mice) showing pulmonary alveolar adenomas in female mice but also nasal respiratory epithelial adenomas and olfactory epithelial neuroblastomas in rats. The metabolism differences reported in the CLH report may not apply in case of exposure by inhalation where no first pass occurs and may deserve to be further discussed.

Dossier Submitter's Response

Thank you for your comment.

Regarding the possibility for carcinogenicity by inhalation please see our response to comment 3 below.
RAC's response
Thank you for your comment. Please see response to comment 3 below.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2019	Switzerland	Federal Food Safety and Veterinary Office FSVO	National Authority	3

Comment received

In the CLH report information on other naphthalene-related compounds regarding the carcinogenic potential focuses mainly on the formation of bronchiolar/alveolar adenomas in mice. In our opinion in the CLH report evidence is lacking why carcinogenic effects like neuroblastoma of the olfactory tissue, which lead to the classification of the structural analogue naphthalene, can be ruled out for 1,4-dimethylnaphthalene, for which no repeated inhalation studies are available.

Naphthalene showed carcinogenic potential in the chronic NTP inhalation study (2002) with F344/N rats, where neuroblastoma of the olfactory tissue in female and male rats have been observed. Proposed mode of action for the finding of neuroblastoma in the olfactory tissue in rats caused by inhalation exposure to naphthalene are the initial metabolism of naphthalene by a CYP enzyme to reactive intermediates (eg expoxides) which lead to GSH depletion, cytotoxicity, inflammation, hyperplasia and eventually tumours in the target tissues (Substance Evaluation Conclusion document EC No 202-049-5 (2018); Summary risk assessment report UK (2003)). Even though human CYP2F is thought to metabolise naphthalene at a lower rate than CYP2F isozyme expressed in rodents, naphthalene has been shown to reduce cell viability and deplete GSH and ATP levels to a greater extent in human cells than in cells from rats and mice in vitro, contradicting the assumption that rodents are more sensitive as humans to naphthalene toxicity (Bogen et al. 2008; Bailey et al. 2015, Kedderis et al. 2014; Substance Evaluation Conclusion document EC No 202-049-5 2018). 1,4-dimethylnaphthalene showed in the present evaluation a lower formation of highly reactive epoxide intermediates compared to 1-methylnaphthalene and 2-methylnaphthalene and the formation of 1,4-dimethyl-methylthionaphthalene by the binding of epoxide intermediates to glutathione. Nevertheless, this does not rule out that 1,4-dimethylnaphthalene is capable to sufficiently deplete GSH leading to inflammation, hyperplasia and eventually to tumour formation in the nasal tissue like the structural analogue naphthalene.

Generally, in our view difficulties arise when comparing the available long-term toxicity studies performed with naphthalene, 1- and 2-methylnaphthalene and 1,4-dimethylnaphthalene due to the different routes of administration and the difference in species sensitivity regarding the finding of neuroblastoma in the olfactory tissue. Concerning naphthalene, the available long term studies have been carried out by inhalation exposure whereas in the available long-term studies investigating the carcinogenic potential of 1,4-dimethylnaphthalene, 1- and 2- methylnaphthalene the compounds have mainly been tested by the oral and dermal route. Moreover, in the long-term studies available in the public literature regarding 1- and 2-methylnaphthalene, mainly mice have been exposed by the oral and dermal route; however, mice exposed by inhalation did not develop olfactory neuroblastoma in the long-term toxicity studies with naphthalene. Moreover, although Lee et al. (2005) showed adverse effects on the olfactory epithelium after intraperitoneal exposure with naphthalene similar to inhalation exposure (Substance Evaluation Conclusion document EC No 202-049-5 (2018)) the 2-year rat study on 1,4-dimethylnaphthalene reference IIA 5.3/01 Doc ID 02-15 (Mallet. 2011) did not report any histopathological examination of the nasal tissue.

Thus, due to the lack of information regarding the carcinogenic potential of 1,4-dimethylnaphthalene on the olfactory epithelium and missing repeated dose studies on inhalation exposure, we propose classification in category 2 for carcinogenicity, based on the available evidence for naphthalene.

Furthermore, we would not entirely support the statement in the CLH report on page 30 regarding the study of Mallet (2011) (reference IIA 5.3/01 Doc ID 02-15) that no test material-related changes were noted for the incidence of neoplasms. Looking at the study report, we observed at the high dose in 2 out of 65 males hepatocellular carcinoma and in 2 out of 62 females cervix leiomyosarcoma. We performed a cochran-armitage trend test and a logistic regression controlling for the body weight, showing a significant trend for hepatocellular carcinoma in male rats and cervix leiomyosarcoma in female rats with p-values between 0.03 and 0.04. We think these findings need to be discussed in the CLH report.

Besides, regarding the finding of neuroblastoma in the olfactory tissue in rats due to inhalation exposure with naphthalene another MoA involving genotoxicity caused by naphthalene metabolites (namely naphthalene-1,2-dioxide, 1,2-naphthoquinone and 1,4-naphthoquinone) has been proposed (Substance Evaluation Conclusion document EC No 202-049-5 (2018)). In view of the negative results in the in vivo genotoxicity studies with naphthalene, this MoA has mainly been excluded. However in our opinion a dual mode of action seems more likely (Bogen, 2008; Substance Evaluation Conclusion document EC No 202-049-5 (2018)). The available in vitro sister chromatid exchange assay, the in vitro UDS and in vivo UDS showed negative results and hence give no indication for a mutagenic potential of naphthalene. However, the UDS-test detects mainly the induction of DNA repair synthesis and is therefore an indicator test detecting DNA damage, not a mutagenicity assay measuring stable genetic alterations (EFSA, Hardy et al., 2017). Thus, the available tests can only give an indication of induced damage to DNA via effects such as unscheduled DNA synthesis (UDS) and sister chromatid exchange (SCE) but no direct evidence of mutation.
Therefore, in our opinion naphthalene has not been sufficiently tested concerning its possible mutagenic potential. The same holds true for 1,4-dimethylnaphthalene, where the positive result of the in vitro mammalian gene mutation assay in mouse lymphoma L5178Ycells has not adequately been addressed in vivo (refer to our comment regarding genotoxicity of 1,4-dimethylnaphthalene). Thus, from the available database a possible genotoxic MoA regarding the carcinogenic potential of 1,4-dimethylnaphthalene cannot be entirely excluded.

References

Bailey et al. (2015) Hypothesis-based weight-of-evidence evaluation and risk assessment for naphthalene carcinogenesis. Crit rev Toxicol: Early Online 1-42
Bogen et al. (2008) Naphthalene metabolism in relation to target tissue anatomy, physiology, cytotoxicity and tumorigenic mechanism of action. Regulatory Toxicology and Pharmacology 51 (2008) S27-S36
Bogen (2008) An Adjustment Factor for Mode-of-Action Uncertainty with Dual-Mode Carcinogens: The Case of Naphthalene-Induced Nasal Tumours in Rats. Risk Analysis, Vol. 28, No. 4
EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger M, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Younes M, Aquilina G, Crebelli R, Gurtler R, Hirsch-Ernst KI, Mosesso P, Nielsen E, van Benthem J, Carfì M, Georgiadis N, Maurici D, Parra Morte J and Schlatter J, 2017. Scientific Opinion on the clarification of some aspects related to genotoxicity asse ssment. EFSA Journal 2017;15(12):5113, 25 pp. https://doi. org/10.2903/j.efsa.2017.5113

Kedderis et al. (2014) Cytotoxicity of naphthalene towad cells from target and non-target organs in vitro. Chemico-Biological Interactions 209 (2014) 85-95
Lee et al. (2005) In situ Naphthalene Bioactivation and Nasal Airflow Cause Region-specific Injury Patterns in the Nasal Mucosa of Rats Exposed to Naphthalene by Inhalation. The Journal of Pharmacology and Experimental Therapeutics JPET 314:103-110
Mallett Jr EJ. (2011). Oral (diet admixture) combined chronic toxicity/carcinogenicity study of 1,4- dimethylnaphtalene in rats. Experimur, Chicago, Illinois USA.
NTP, N.T.P. (2000). Toxicology and Carcinogenesis Studies of Naphthalene (CASD No. 91-20-3) in F344/N Rats (Inhalation Studies). National Toxicology Program. Rockville, MD: US Department of Health and Human Services, National Institutes of Health.
United Kingdom. (2003). European Union - Risk Assessment Report - Naphthalene. European Chemicals Bureau, European Communities. SUBSTANCE EVALUATION CONCLUSION
United Kingdom. (2018). SUBSTANCE EVALUATION CONCLUSION as required by REACH Article 48 and EVALUATION REPORT for Naphthalene. EC No 202-049-5

Dossier Submitter's Response

Thank you for your comments.

Indeed it is difficult to compare the toxicity profile of 1,4-DMN with naphthalene due to differences in the route of administration. The CLH report was based on the information available for 1,4-DMN which did not include an inhalation carcinogenicity study. Therefore, carcinogenicity via inhalation cannot be fully excluded. However, as indicated in the comment the proposed mode of action for the neuroblastoma of the olfactory tissue is metabolism of naphthalene to reactive intermediates, such as epoxides, leading to GSH depletion, cytotoxicity, inflammation, hyperplasia and eventually tumours. Since ring hydroxylation via reactive epoxide is a minor metabolic route is compared to other naphthalene compounds such as 1,2-dimethylnaphthalene it is less likely that 1,4-DMN will also form neuroblastoma. We would therefore propose to conclude that 1,4-DMN is not carcinogenic via the oral route and that data is lacking for the inhalation route.

Regarding your comment on the mutagenicity data for 1,4-DMN please see our response to comment 4.

RAC's response

Thank you for your comments and response. RAC agrees with the lack of data by inhalation.
RAC considers that the data are insufficient to conclude that the effects observed with 2-MN or naphthalene are less likely for 1,4-DMN. There are too many uncertainties in the quantitative comparison of the formation of ring hydroxylation *via* reactive epoxide:
- the studies on 2-MN and 1,4-DMN were only performed following acute exposure,
- the studies were not performed by the same route of exposure (ip and oral for 1,4-DMn and subcutaneous for 2-MN)
- only a low concentration was tested by oral route with 1,4-DMN (28 mg/kg)
- naphthalene metabolism pathway is different from the alkylated naphthalene compounds.

For mutagenicity, please see response to comment 4.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	France		MemberState	4
Comment received				
FR: 10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity page 28. Positive results were observed in the in vitro mammalian cell gene mutation test (Study 3) in presence of metabolic activation and the in vitro UDS is considered equivocal. However, there is no relevant in vivo test to follow up the positive results in the in vitro gene mutation assay, available. Indeed, the in vivo MN test investigates clastogenicity and aneugenicity and not gene mutation and the in vivo UDS test is generally not considered sufficiently sensitive to overrule positive results in in vitro gene mutation tests. Additionally, in the UDS in vivo test performed on 1,4-dimethylnaphthalene, one of the positive controls failed the acceptance limits for a positive control response which challenges furthermore the sensitivity of the test system. Therefore, based on the available data, uncertainties remain as regard mutagenic potential of 1,4-dimethylnaphthalene.				
Dossier Submitter's Response				
Thank you for your comment. At the time that the dossier was submitted for active substance approval as plant protection product in 2008 the *in vivo* UDS was the study which was generally required as follow-up to a positive *in vitro* gene mutation study. No OECD guidelines were available yet for an *in vivo* Comet assay or transgenic rodent assay. For the CLH submission we relied on the data that was available in the DAR for 1,4-dimethylnapthalene. We do agree that nowadays the *in vivo* UDS is no longer considered sufficient as a follow up study and this will have to be addressed during the renewal of the active substance. For now we would propose that the data is lacking to conclude on the mutagenic potential of 1,4-dfimethylnaphthalene.				
RAC's response				
Thank you for your comments. RAC agrees with DS's response. Moreover, as detailed in the RAC opinion, the reliability of the UDS study is questionable.				

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2019	Switzerland	Federal Food Safety and Veterinary Office FSVO	National Authority	5
Comment received				
In the in vitro mammalian gene mutation assay in mouse lymphoma L5178Y cells with 1,4-dimethylnaphthalene a dose related increase in mutant frequency exceeding the historical control was observed in the presence of S9 (reference IIA 5.4/03 Doc ID 424711). This positive result in vitro has not been followed-up properly in vivo. The only in vivo follow-up is a USD-test, which has been negative. The UDS-test detects mainly the induction of DNA repair synthesis and is therefore an indicator test detecting DNA damage, not a mutagenicity assay measuring stable genetic alterations (EFSA, Hardy et al., 2017). Corresponding with the positive result observed in vitro the in silico SARpy mutagenicity model in the VEGA (Q)SAR platform predicts for 1,4-dimethylnaphthalene a mutagenic potential as well (REACH Annex III Inventory.) Similar the Danish (Q)SAR database				

predicts in the models CASE Ultra and Leadscope a positive result for in vitro mutations in thymidine kinase locus in mouse lymphoma cells and unscheduled DNA synthesis (UDS) in rat hepatocytes as well as in vivo a positive result in the Comet Assay in mice.
The weight of evidence available does not primarily suggest the induction of DNA repair synthesis as a mode of action for the observed mutagenicity in vitro, thus in our opinion the positive result of the in vitro mammalian gene mutation assay in mouse lymphoma L5178Ycells has not adequately been addressed in vivo and therefore without further investigations a mutagenic potential for 1,4-dimethylnathalene cannot be excluded. We would therefore propose classification for mutagenicity category 2.

References
EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger M, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Younes M, Aquilina G, Crebelli R, Gurtler R, Hirsch-Ernst KI, Mosesso P, Nielsen E, van Benthem J, Carfì M, Georgiadis N, Maurici D, Parra Morte J and Schlatter J, 2017. Scientific Opinion on the clarification of some aspects related to genotoxicity asse ssment. EFSA Journal 2017;15(12):5113, 25 pp. https://doi. org/10.2903/j.efsa.2017.5113

Dossier Submitter's Response
Thank you for your comment. Please see our response to comment number 4.
RAC's response
Thank you for your comment. Please see our response to comment number 4.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22.05.2019	Germany		MemberState	6

Comment received

a) Adverse effects on developmental toxicity
In the EOGRTS a statistically significant delay in preputial separation in the mid dose (160 mg/kg bw/d) and high dose (510 mg/kg bw/d) males and vaginal patency in the high dose (510 mg/kg bw/d) females was observed. Due to following reasons no classification for developmental toxicity was proposed by the dossier submitter:
1. The effects occurred in the presence of maternal toxicity, which means reduced body weights (-15 %), reduced body weight gain (-30 %), reduced food consumption (-61 %, day 3), increased cholesterol, gamma-GT and triglycerides, and increased liver, spleen and adrenal weight in the high dose group.
However, it is not documented which values at what time of the study were considered for the calculation of body weight (gain) reduction. We would appreciate if the dossier submitter could deliver detailed quantitative information on body weight, body weight gain and food consumption throughout the study period for females. Generally please provide all absolute values and not only selected percentages. This is necessary to be able to conclude if the delay in puberty is secondary to maternal toxicity or not.
2. The finding seems to be related to a reduced body weight of the pups.
However, the pup body weight at preputial separation and vaginal patency at the high dose group was reduced by 11 % compared to control group. In our view, this slight reduced pup weight would not cause the delayed puberty.
3. The delay in preputial separation (PND 46 in high dose group vs. PND 37 in control group) was within the historical control data (mean PND 44.7, range PND 41-50). It has to be noted that the control values in the study are lower than the historical control values.
However, the historical control data for preputial separation are based on a low number of evaluated male rats with N = 46. Therefore, the concurrent control group should be given

a higher weight than the historical control data.
Historical control data for vaginal patency were not provided.

Furthermore, according to CLP Regulation (Annex I, 3.7.1.3), adverse effects on onset of puberty results in classification for effects on sexual function and fertility. Therefore, a discussion regarding classification for adverse effects on sexual function and fertility rather than developmental toxicity should be considered by RAC.

b) Effects on or via lactation
In the EOGRTS, the severity of litter body weight reduction increased throughout the lactation period. In the high dose group the litter body weight at birth was statistically significant reduced by 8 %, at PND 4 by 21-22 % and PND 14 by 45-56 %. The dossier submitter considered these findings as secondary to maternal toxicity (details described above) and therefore, no classification for adverse effects on or via lactation was proposed. As mentioned above, we would appreciate if the dossier submitter could deliver detailed information on body weight, body weight gain and food consumption for females to conclude if the increased litter weight reduction throughout the lactation period is secondary to maternal toxicity or not. Furthermore, we kindly ask the dossier submitter to explain the calculations of litter body weights. The severe litter body weight reduction at the high dose is possibly due to the fact that pups have died.

Dossier Submitter's Response

Thank you for your comment.

1) More detailed result tables on the maternal toxicity is included in the tables below. Reduced body weight was observed in high dose females throughout the entire study.

Table 1: Body weight in parental females (g)

Study day	Dose group (ppm)			
	0	**500**	**2000**	**7500**
Pre-mating				
0	212	212	215	212
3	216	218	216	**195* (-9.8%)**
7	225	225	223	**204* (-9.3%)**
14	233	233	230	**217* (-6.9%)**
Gestation				
0	234	234	228	**214* (-8.5%)**
7	257	258	250	**228* (-11.2%)**
14	282	285	278	**248* (-12.1%)**
21	363	366	353	**307* (-15.4%)**
Lactation				
0	278	275	271	**240* (-13.7%)**
4	287	284	276	**229* (-20.2%)**
7	299	297	288	**233* (-22.1%)**
14	307	308	299	**246* (-19.9%)**
21	299	299	296	**253* (-16.4%)**

*Significantly different from control p≤0.05

Table 2: Body weight gain in parental females (g)

Study day	Dose group (ppm)			
	0	**500**	**2000**	**7500**
Pre-mating				
0-3	4	6	1	**-18***
3-7	9	7	7	9
7-14	9	8	7	**13***

0-14	21	21	15	**4***
Gestation				
0-7	23	24	22	**14***
7-14	25	27	28	**20***
14-21	85	88	82	**60***
0-21	134	139	136	**93***
Lactation				
0-4	9	7	5	**-11***
4-7	12	13	12	3
7-14	9	11	11	12
14-21	-9	-9	-3	**9***
0-21	20	23	25	**12***

*Significantly different from control p≤0.05

Table 3: Food consumption in females (g)

Study day	**Dose group (ppm)**			
	0	**500**	**2000**	**7500**
Pre-mating				
3	46	48	41	**18* (-60.9%)**
7	73	76	68	**54* (-26.0%)**
14	124	117	122	122
Gestation				
7	134	142	123	**101* (-24.6%)**
14	138	148	130	**116* (-15.9%)**
21	164	151	**141* (-14.1%)**	**122* (-25.6%)**
Lactation				
4	152	141	128	**69* (-54.6%)**
7	152	155	134	**73* (-52.0%)**
14	392	391	382	**218* (-44.4%)**
21	629	575	**502* (-20.2%)**	**288* (-54.2%)**

*Significantly different from control p≤0.05

Table 4: Clinical chemistry findings in parental females

Parameter	**Dose group (ppm)**			
	0	**500**	**2000**	**7500**
A/G ratio	1.0	1.1	**1.1***	**1.2***
ALP [U/L]	66	65	67	**81***
BUN [mg/dL]	201	19	19	**16***
CHOL [mg/dL]	42	51	**68***	**94***
CREA [mg/dL]	0.38	0.36	**0.33***	**0.32***
GLU [mg/dL]	121	181	137	**143***
PO4 [mg/dL]	7.0	7.2	6.8	**5.3***
GGT [U/L]	0.2	0.0	0.4	**3.1***
Na [mmol/L]	142	142	141	**139***
TRIG [mg/dL]	36	46	**53***	**51***

*Significantly different from control p≤0.05

Table 5: Organ weight in parental females

Parameter	**Dose group (ppm)**			
	0	**500**	**2000**	**7500**
Adrenals - absolute	0.081	0.078	**0.069* (-14.8%)**	**0.061* (-24.7%)**
Adrenals - relative	0.031	0.030	0.027	**0.026* (-16.2%)**
Liver - absolute	8.29	8.60	9.38	**11.73* (+41.5%)**
Liver - relative	3.18	3.30	**3.68* (+15.7%)**	**5.01* (+57.5%)**
Spleen - absolute	0.675	0.693	0.610	**0.527* (-21.9%)**
Spleen - relative	0.258	0.266	0.240	**0.226* (-12.4%)**

*Significantly different from control p≤0.05

2) We consider that since a body weight reduction of >10% is observed at the time of preputial separation in male pups and vaginal patency in female pups at the high dose is indicative that the observed effect is due to a general growth delay relating to the maternal toxicity and not due to a direct effect of 1,4-DMN on sexual development. Further support for this is that no effect on endocrine sensitive organs, such as uterus, ovary, testes or seminal vesicles weight, was observed in the extended one-generation study. Therefore, the DS considers that no classification is required on the basis of the observed effect. 3) The DS considers that the information is sufficient to conclude that the effect on vaginal patency and preputial separation is due to a general growth delay and not a direct effect of 1,4-DMN (see also point 2).
RAC's response
Thank you for your comment and response. RAC agrees that the observed delayed growth effects were not due to a direct effect of the substance.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.05.2019	Germany		MemberState	7
Comment received				
We agree with the proposed classification Eye Irrit. 2, H319 based on conjunctival oedema (mean score ≥ 2) in 5 out of 6 animals observed in an eye irritation study.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	France		MemberState	8
Comment received				
FR: The proposal for classification: Eye Irrit. 2 H319 is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2019	Switzerland	Federal Food Safety and Veterinary Office FSVO	National Authority	9
Comment received				
In our opinion the possible concern regarding haemolytic anaemia should be addressed in the CLH report of 1,4-dimethylnaphthalene. Regarding naphthalene, evidence from humans drives the concern for haemolytic anaemia since the main experimental species (rats, mice and rabbits) do not appear to be				

a suitable model for this effect (Substance Evaluation Conclusion document EC No 202-049-5 (2018)). Regarding naphthalene, the only animal study showing evidence for haemolytic anaemia was the oral acute toxicity study with dogs (Zuelzer and Apt, 1949; Substance Evaluation Conclusion document EC No 202-049-5 (2018)).
Individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) may be more susceptible to the haemolytic effects of naphthalene than others in the general population (Substance Evaluation Conclusion document EC No 202-049-5 (2018)). Around 4% of the European population may have the G6PD deficiency making them more susceptible to naphthalene induced haemolytic anaemia (Substance Evaluation Conclusion document EC No 202-049-5 (2018)).
1,4-dimethylnaphthalene has not been tested in dogs. Moreover, evidence regarding naphthalene suggest that the available database for 1,4-dimethylnaphthalene concerning animal studies (rats, mice and rabbits) will not be suitable to identify haemolytic anaemia. Clinical cases were not reported in the draft assessment report and proposed decision of the Netherlands prepared in the context of possible inclusion of 1,4-dimethylnaphthalene in Annex I of council directive 91/414/ECC. However, compared to naphthalene the database for 1,4-dimethylnaphthalene concerning human incidences is very small. Thus, we would propose for 1,4-dimethylnaphthalene classification for specific target organ toxicity category 2 via repeat exposure from the available database of naphthalene, where human lethal dose was assumed at 100 mg/kg bw (Substance Evaluation Conclusion document EC No 202-049-5 (2018)).

References
United Kingdom. (2018). SUBSTANCE EVALUATION CONCLUSION as required by REACH Article 48 and EVALUATION REPORT for Naphthalene. EC No 202-049-5
Rapporteur Memberstate: Netherlands. (2012). 1,4-Dimethylnaphatlene - Volume 3 - Annex B - Rapporteur Memberstate: The Netherlands - March 2012 - Draft Assessment Report and Proposed Decision of the Nederlands prepared in the context of the possible inclusion of 1,4-dimethylnaphtalene in Annex I of the Council Directive 91/414/EEC.

Dossier Submitter's Response

Thank you for your comment.

For the CLH report we relied on the information that was available in the Draft Assessment Report for 1,4-DMN. On the basis of the information that is available 1,4-DMN does not need to be classified for STOT-RE. However, we do acknowledge that this conclusion is based on data in rodents which are known to be a poor model for haematotoxicity of naphthalene. It is noted that although there was some evidence of haematotoxicity with naphthalene in dogs that this study was poorly conducted and it was indicated that there is some doubt whether there are suitable animal models available for this endpoint (Substance Evaluation Conclusion document EC No 202-049-5 (2018)). It is therefore difficult to adequately address the possibility of haematotoxic effects of 1,4-DMN.
As a side note, as nearly all case reports of haematotoxicity of naphthalene concerned single events of incidental exposure, STOT SE would be more applicable to this effect.

No cases of haemolytic anemia have been reported in humans due to 1,4-DMN exposure. In conclusion, the DS remains of the opinion that the available information does not warrant classification for STOT RE or STOT SE.

RAC's response

Thank you for your comment and response.

The read-across between naphthalene and 1,4-DMn is not supported as major differences in TK has been identified. On the basis of the available data on 1,4-DMN, no classification is warranted.

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.05.2019	Germany		MemberState	10
Comment received				
We agree with the proposed classification Asp. Tox 1, H304. 1,4-dimethylnaphthalene is a hydrocarbon and has a kinematic viscosity < 20.5 mm²/s measured at 25 °C.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	France		MemberState	11
Comment received				
FR: The proposal for classification: Asp. Tox. 1 H304 is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
29.05.2019	Germany	<confidential>	Company-Manufacturer	12
Comment received				
Chapter 11.7.2 (Long-term aquatic hazard): The classification of the long-term hazard is based on the NOEC values of 0.03 mg/L (algae) and 0.09 mg/L (fish), leading to category Aquatic Chronic 2 (H411). However, the Guidance on the application of the CLP criteria (ECHA, Version 5.0, July 2017, p. 493, chapter 4.1.3.1.1.) states that for chronic studies, the EC10 (when available) should be preferred over the NOEC. Therefore, re-calculations of the test results on Pseudokirchneriella subcapitata (DocID 535A-102, see attachment '1,4 DMN_ 535A-102_ToxRat_Algae.pdf') and Oncorhynchus mykiss (DocID 535A-105, see attachment '1,4 DMN_535A-105_ToxRat_Fish_JGT') have been performed. The results are: ErC10 = 0.357 mg a.s./L for algae, and EC10 = 0.200 mg a.s./L for fish. Hence, both EC10 values are above 0.1 mg a.s./L., leading to a classification into Category Aquatic Chronic 3 (H412). ECHA note – An attachment was submitted with the comment above. Refer to public attachment 1,4DMN_CLHcomm_calculations.zip				
Dossier Submitter's Response				
Thank you for your comment.				

For the CLH report we relied on the information that was available in the Draft Assessment Report for 1,4-DMN and at the time did not look at the possibility to calculate the EC_{10}. However the company/manufacturer is correct that for chronic studies, the EC_{10} (when available) should be preferred over the NOEC. Consequently the key endpoint for long-term aquatic hazard is the NOEC of 0.16 mg a.s./L for *Daphnia magna*. With the substance being considered rapidly degradable this leads to classification as Aquatic chronic 3.

RAC's response

Regarding the validity of the algal test and RAC's conclusion to only consider valid the results at 48h of exposure, please see RAC response to comment no. 14.
RAC agrees with the company/manufacturer's comment and the DS's response that according to the current ECHA Guidance on the application of the CLP criteria (Version 5.0, July 2017), when EC10 values are available these are preferred over NOEC values in chronic toxicity studies. RAC notes that this applies in cases where EC_{10} and NOEC values are available for the same endpoint. RAC considers more appropriate to use EC_{10} values for aquatic chronic classification because NOEC values strongly depend on the experimental design (number of doses, width of the inter-dose interval, etc.), whereas EC10 values are derived from the whole concentration-response curve.

Therefore, in RAC's opinion, the new EC_{10} values provided by the company/manufacturer are acceptable, and consequently, the relevant chronic values available for fish and algae are the 28d-EC_{10} of 0.200 mg/L for Oncorhynchus mykiss and the 48h-E_rC_{10} of 0.232 mg/L for Pseudokirchneriella subcapitata, respectively, even though these are significantly higher than the respective NOEC values. For the available Daphnia magna study only NOEC values are reported, and hence, they are used for classification.

In conclusion, based on the available chronic toxicity data on 1,4-DMN for three trophic levels, RAC considers that the lowest valid chronic toxicity value is the 21d-NOEC of 0.16 mg/L for Daphnia magna. This is below the classification threshold of 1.0 mg/L for Aquatic Chronic 3 for rapidly degradable substances.

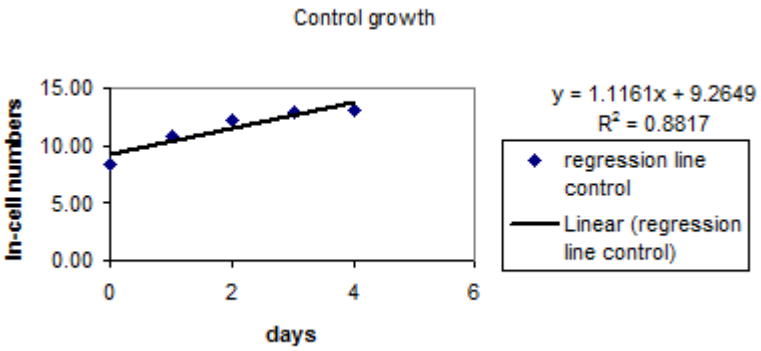
Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	France		MemberState	13
Comment received				
FR agrees with the classification for environmental hazard and with the acute M factor proposed in the CLH report.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. Please see the response to comment no. 12.				

Date	Country	Organisation	Type of Organisation	Comment number
24.05.2019	Belgium		MemberState	14
Comment received				
BE CA thanks RIVM for the proposal of harmonised classification. BE CA supports the proposal to classify 1,4-dimethylnapthalene for the environment with Aquatic Acute 1, H400 (M=1) and Aquatic Chronic 2, H411. The algae test with Pseudokirchneriella subcapitata is considered reliable and acceptable				

for classification by de dossier submitter. However we do not agree with this as validity criteria of the test (OECD, 2001) are not met.
Furthermore pH of the control was increased by more than 1.5 units during the study.
The use of a sealed exposure system in the algal growth inhibition test will result in culture growth being limited by CO2 depletion and increasing pH and the results should be interpreted with caution.
Nevertheless , the results of this algae study (72hNOEC=0.03mg/L) are in the same order of magnitude than fish (28dNOEC= 0.09 mg/L).

Dossier Submitter's Response

Thank you for your comment.
In the DAR we had the following points and in the end a little addition after the conclusion.
pH increased with > 1.5 unit in the control, solvent control and at 0.030, 0.053, 0.11, and 0.21 mg as/L, due to excessive cell growth. This is not considered to have influenced the result. The validity criteria of OECD 201 (2001) are not met with respect to control growth. No exponential growth rate in the control. The mean variance of daily growth rate in the control was > 35% (mean value 79%).



<u>The remarks above were addressed by the notifier with the following statement (summarised):</u>
• The test started with 5000 cells/ml and had reached the control criteria (16X or 80,000 cells/ml) by 48 hours and was just short of the 96-hour control criteria (500,000 cells/ml) at both 72 hours and 96 hours. This study was conducted according to the OECD 201, adopted July 1984, in which the validity criteria was that cell concentration in the control cultures should have increased by a factor of at least 16 within three days.
• Due to volatility of the test substance and a desire to maintain test concentrations throughout the study, the test was done in a closed system with limited headspace. Due to the lack of gas exchange in this testing environment, algal growth is limited. The algae growth was exponential during the first 48 hours but quickly outgrew the carrying capacity of the media. Growth peaked very quickly so the algae were past logarithmic growth phase by 72 hours. However, the study did meet the protocol and the OECD 201 growth criteria that were in effect at the time.
• We agree that the mean variance of growth rate in the control was 79% at 96-hours. However, the OECD 201 (2006) guideline recommends 35% at 72-hours. In this study, the mean variance of growth rate was 58% at 72 hours and 41% at 48 hours at the time that the cell growth had peaked.
• The observed effects of 1,4-DMN on green algal were evident and consistent at 48, 72 and 96
hours. These effects were observed during the early portion of the test when exponential growth was occurring as well as at 72 and 96-hours, after cell growth had peaked. The

failure to have exponential growth between 48 and 72 hours did not change the conclusion of the test.
- The results of the test showed a clear dose-response relationship between algal growth and mean measured concentrations of 1,4-DMN, which were maintained between 90 and 110% of nominal concentrations throughout the test.

Conclusion RMS: The test result will be used for risk assessment in a weight of evidence approach.

However, after peer review of the DAR, the following data requirement was set.:

Data requirement: 5.2
Applicant to provide 48-hour EC_{50} values from the algae study (Desjardins *et al.* (2002)) and also demonstrate that there was 16 fold exponential increase within 48-hours. If the 48-hour values are lower then the 72- and 96-hour values, then the 48-hour values should be used in an updated risk assessment.

This is adressed with the following tables from the study report of Desjardins et al (2002):

Table 5

Mean Cell Density and Percent Inhibition

Mean Measured Test Concentration (mg a.i./L)	24 Hours		48 Hours		72 Hours		96 Hours	
	Mean Cell Density (cells/mL)	Percent Inhibition[1]	Mean Cell Density (cells/mL)	Percent Inhibition[1]	Mean Cell Density (cells/mL)	Percent Inhibition[1]	Mean Cell Density (cells/mL)	Percent Inhibition[1]
Negative Control	51,514	--	200,578	--	391,009	--	497,796	--
Solvent Control	52,544	--	180,023	--	370,746	--	482,356	--
Pooled Control	52,029	--	190,301	--	380,878	--	490,076	--
0.030	45,751	13	172,188	4.4	371,166	-0.11	432,914*	10
0.053	45,812	13	178,151	1.0	317,084*	14	412,501*	14
0.11	40,070	24	165,337	8.2	300,007*	19	383,192*	21
0.21	36,709	30	133,279	26	252,101*	32	310,739*	36
0.44	23,315	56	52,729	71	130,457*	65	157,582*	67
0.86	10,671	80	13,756	92	13,328*	96	10,681*	98

[1] Percent Inhibition was calculated relative to the solvent control replicates using SAS Version Eight. Manual calculations may differ slightly.
* Statistically significant difference ($p<0.05$) at 72 and 96 hours from the solvent control replicates using Dunnett's test.

Table 5 shows that after 48 hrs the cells in the solvent control had increased 36-fold, adressing the concern about the criteria of 16-fold increase after 48 hrs.

Table 8

EC50, E_bC50 and E_rC50 Values Over the 96-Hour Exposure Period

Time	Cell Density		Area Under the Growth Curve (Biomass)		Growth Rate	
	EC50 (mg a.i./L)	95% Confidence Interval (mg a.i./L)	E_bC50 (mg a.i./L)	95% Confidence Interval (mg a.i./L)	E_rC50 (mg a.i./L)	95% Confidence Interval (mg a.i./L)
24 Hours	0.40	0.32 and 0.49	0.35	0.28 and 0.43	0.63	0.57 and 0.69
48 Hours	0.32	0.30 and 0.34	0.32	0.30 and 0.35	0.58	0.55 and 0.61
72 Hours	0.34	0.30 and 0.38	0.32	0.30 and 0.35	0.62	0.60 and 0.64
96 Hours	0.34	0.30 and 0.38	0.33	0.30 and 0.36	0.60	0.58 and 0.62

In table 8 the EC50 values for the different time scales are shown. Values are considered acceptable by RMS. The 48 hr EC50-values are not statistically different from the 72 hr values.
On the basis of these facts we consider the test sufficiently reliable for classification purposes.

RAC's response

RAC agrees with the BE MSCA that the available algal test does not fulfil the validity criterion regarding the mean coefficient of variation of section-by-section growth rates in control groups of the OECD TG 201 after 72 and 96 hours of exposure. RAC also notes that the pH had increased by more than 1.5 in most of the treatment groups and controls after 96 hours.

According to ECHA Guidance R.7b, if in an algal growth inhibition test the exponential growth ceased in the control before the end of the test period, only data from the part of the test where exponential growth occurs and the validity criteria for the controls are fulfilled, should be used. Furthermore, in the OECD TG 201 it is indicated that normally the test duration is 72h but the test period may be shortened to at least 48 hours to maintain unlimited, exponential growth during the test as long as the minimum multiplication factor of 16 is reached and the other validity criteria of the guideline are fulfilled. Therefore, the results at 72 hours should not be considered valid for classification.
As indicated by the dossier submitter, 16-fold increase of cell density was reached by 48 hours in the controls. RAC notes that based on the information in the full study report, the cell density of each replicate was not measured daily during the 4 days test period but instead at each sampling (every 24 hours during 4 days) 3 replicates per treatment and control group were sacrificed and their cell densities measured. Therefore, it is not possible to determine section-by-section growth rates for each replicate and the mean coefficient of variance for those growth rates as indicated in the OECD TG 201. It is not clear for RAC how the "mean variance values for daily growth rates" mentioned in the CLH report were calculated. To be able to assess whether the second validity criterion of the OECD 201 guideline was met, RAC calculated the section-by-section growth rates based on the mean cell densities measured for the 3 replicates per control group at each sampling, and determined the coefficient of variation (CV) for these growth rates. This resulted in CV values of 26 % and 31 % for blank and solvent controls, respectively, when considering only the first 48 hours of the test and in a CV value of 47 % for both controls when considering 72 hours test duration. Hence, based on these values, at 72 hours the validity criterion of the guideline is not met whereas at 48 hours it was met.

RAC also calculated based on the raw data that the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was ≤ 7 %. Therefore, RAC concluded that the validity criteria of the OECD 201 guideline are met at 48 hours of exposure, and hence, results of the study at 48h can be considered acceptable for classification. The 48h-E_rC_{50} was included in the original study report and 48h-NOE_rC and 48h-E_rC_{10} values have been calculated based on the raw data and provided by a company/manufacturer during the public consultation.

Please see also the response to comment no. 12 regarding why the EC_{10} values provided during the public consultation are preferred over the NOEC values in the case of the available chronic fish and algal studies, and the conclusion on the environmental chronic classification.

Date	Country	Organisation	Type of Organisation	Comment number
31.05.2019	United Kingdom		MemberState	15

Comment received

1,4-dimethylnaphthalene (EC: 209-335-9; CAS: 571-58-4)

Rapid degradability:
We note that the key study was not conducted to GLP and some study limitations are described in the CLH e.g. lack of abiotic control and limited observation points. Is it possible to provide details of the inoculum and confirm if study validity criteria were met? Such details are relevant to assess if the study is reliable to consider the substance as rapidly degradable. In addition, are supporting data available to support rapid degradation i.e. QSAR outputs or analogue data such as 1,3-dimethylnapthalene used for the bioaccumulation endpoint?

Ecotoxicity:
We consider that the algal growth inhibition study using Pseudokirchneriella subcapitata study is not reliable for hazard classification due to limitations with the controls. We agree that the closed test system is likely to have impacted growth and that the controls meet the overall cell growth x16 fold at 48 and 72 hours. However, noting the CoV for the section-by-section specific growth rate of 41% at 48 hours (which is greater than current validity criteria 35%) we do not think exponential growth was occurring over the whole initial 48 hour period. We appreciate the study met the test guideline validity criteria at the time it was performed but study controls are crucial to test validity and the current OECD TG 201 validity criteria demonstrate the study controls were not performing adequately. Therefore, we do not consider the study can be used for hazard classification. We wonder if there are suitable analogue data that can be presented to consider toxicity to algae, e.g. for the 1,3-dimethylnapthalene analogue used for the bioaccumulation endpoint?

The next lowest chronic endpoint is the Oncorhynchus mykiss 28 d growth NOEC at 0.09 mg a.s./L (mm). This endpoint is in the same concentration range as the P. subcapitata endpoint, resulting in the same classification as Aquatic Chronic 2 for this rapidly degradable substance. We note this chronic fish endpoint is from an OECD TG 215 study and that growth may not be the most sensitive endpoint. This may be the case given the short 4 day FELS NOEC of <0.67 mg/l based on mortality and embryo abnormalities. As such, it may be appropriate to consider the surrogate approach using the acute toxicity to fish endpoint (LC50 0.67 mg/l).

Dossier Submitter's Response
Thank you for your comment. Where it concerns the key study on degradability, it is assessed that the test was valid conform Guideline OECD 301C = EEC C.4-F. and the substance was shown to be readily biodegradable. Concerning Pseudokirchneriella subcapitata see comment (nr.14) of Belgium and the response. Concerning the chronic endpoint see comment (nr.12) of a Geman company/manufacturer and the response. Please note that the surrogate approach is only applicable to not-rapidly degradable substances and cannot be applied since 1,4-dimethylnaphthalene is a rapidly degradable substance.
RAC's response
Rapid degradability: RAC acknowledges that the available OECD 301C (MITI I) test has some deviations from the guideline, e.g. lack of abiotic control, and is not conducted in accordance with GLP. Regarding further details on the inoculum, RAC notes that in the annex of the CLH report it is only mentioned that in the inoculum control group 30 mg/kg activated sludge from CITI, Japan, was used. It can be assumed that the same concentration is used in the bottles with the test substance. Furthermore, RAC considers that since the inoculum originated from CITI (Chemical Inspection and Testing Institute) Japan, it is likely to have been suitable for an OECD 301 C (MITI-I) test. Regarding the fulfilment of validity criteria of the guideline, based on the information in the CLH report and its annex, the reference substance reached the required degradation levels after 7 and 14 days, and the difference of the extremes of replicate values of the removal of the test substance at the end of the test was less than 20 %. There is no information on the oxygen consumption of the blank control or on the pH of the test media, so it is not possible to assess whether the validity criteria indicated in the guideline regarding these aspects were met. However, it is noted that the oxygen uptake of the test solution was corrected for uptake of blank inoculum and it could be expected to have been in the normal range since there is no mentioning otherwise. Regarding the lack of abiotic control, RAC notes that if part of the test substance was lost from the test vessels by volatilisation, it would mean that the BOD, and consequently, the degradation of the test substance, were underestimated because the BOD was calculated considering the initial test substance concentration. Therefore, since the degradation of the test substance reached the pass level, the lack of abiotic control does not affect the conclusion of the study. In conclusion, RAC considers that the study can be considered valid and acceptable for classification, and since the substance reached the pass level for ready biodegradation in the study, it can be considered rapidly degradable for classification purposes. Ecotoxicity: Regarding the validity of the algal test, please see RAC's response to comment no. 14. Regarding the fish chronic toxicity data and the proposal to use surrogate approach, RAC disagrees with the DS's claim that the surrogate approach can only be used for non-rapidly degradable substance. According to the CLP, the surrogate approach can be used if the substance is non-rapidly degradable and/or bioaccumulable. Since 1,4-DMN is considered bioaccumulable for classification purposes, it is possible to use the surrogate approach, if considered that adequate chronic data is not available for all three trophic levels. RAC notes that based on ECHA Guidance R.7b, OECD TG 215 is considered a relevant test for assessing chronic toxicity to fish. The available OECD 215 test with 1,4-DMN is considered valid and acceptable for classification purposes. RAC agrees that based on the available test with cod eggs performed partly in accordance with OECD 210, the

substance may have effects in the reproduction of fish, and hence, it cannot be excluded that growth may not be the most sensitive endpoint for chronic toxicity. However, it is not possible to evaluate the reliability of the cod eggs study due to lack of detailed information. Therefore, RAC is of the opinion that there is not enough justification to consider that the available chronic fish data is not adequate and use surrogate approach instead in the chronic classification.

Please see also the response to comment no. 12 regarding why the EC_{10} values provided during the public consultation are preferred over the NOEC values in the case of the available chronic fish and algal studies, and the conclusion on the environmental chronic classification.

PUBLIC ATTACHMENTS
1. 1,4DMN_CLHcomm_calculations.zip [Please refer to comment No. 12]