Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

N,N-diethyl-m-toluamide; deet

EC Number: 205-149-7
CAS Number: 134-62-3

CLH-O-0000001412-86-161/F

Adopted

9 June 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON N,N-DIETHYL-M-TOLUAMIDE; DEET

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.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: N,N-diethyl-m-toluamide; deet
EC number: 205-149-7
CAS number: 134-62-3
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2016	Belgium		Member State	1
Comment received				
References are made to the final CAR of March 2010. However this CAR was not annexed. Furthermore it is said that a large dataset is available for DEET but not all those environmental studies are reported in the CLH report. Furthermore, an in depth description of the degradation studies is not given in the CLH report. As degradation potential is crucial in the environmental declassification of DEET it is difficult to decide on the environmental classification.				
Dossier Submitter's Response				
The assessment report for DEET can be downloaded from the ECHA dissemination site. More detailed information on the findings in key studies discussed in the CLH report is available in the robust study summaries included as a confidential attachment in IUCLID. This approach was taken to compromise between extensive confidentiality claims made by the applicant for the biocides review (providing the majority of studies) and the necessity for Member States and members of RAC to make an independent and transparent review of data. Our decision was to take the most relevant environmental studies for the classification proposal of DEET. For the degradation studies for DEET there is a description of the key study on the ready biodegradability study according to the OECD guideline 301 B. Since this a standardized degradation test highly recommended for classification purpose of ready biodegradability and the test was reliable, we decided to use it as a key study. The other degradation studies with lower reliability and with contradicting results on the degradation, we did give information and a discussion in the CHL report and the reason why we did not use them as key studies.				

RAC's response
RAC is of the opinion that even with the assessment report and robust study summaries the dataset for DEET is not large. In depth descriptions of the degradation studies would have been useful to strengthen the classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
10.08.2016	Germany		Member State	2
Comment received				
The German CA agrees with the proposed classification of N,N-diethyl-m-toluamide; deet as: Acute Tox. 4, H302 Skin Irrit. 2, H315 Eye Irrit. 2, H319 In view to substance identity we would like to add following comment: In IUCLID section 1.2 two impurities are only identified by their IUPAC name. Please add the missing CAS identification.				
Dossier Submitter's Response				
Thank you for informing us about your position. Since the IUCLID dossier will not be updated at this stage of the process and taking into account that this is confidential business information, CAS numbers for the two impurities can be provided in a separate document-if considered necessary for the assessment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United States	DEET EU Joint Venture (DEET EUJV)	Industry or trade association	3
Comment received				
The DEET EUJV greatly appreciates the opportunity to provide their comments. With regard to additional hazard classes assessed in CLH report, the DEET EUJV agrees with the proposed non-classification for the other hazard classes assessed in the CLH report. (Please see page 2 of submitted comments). With regard to the overall classification, the DEET EUJV strongly disagrees with the inclusion of hazard classes not assessed in the current CLH report but proposed for future entry in Annex VI, CLP Regulation. For an insect repellent that is applied on the skin by consumers, the review of skin and eye irritation data should be of particular priority for its harmonised classification and labelling (see detailed review in Annex below). Based on the available toxicological data and the criteria of the CLP Regulation, the DEET EUJV proposes the following entry for DEET: Acute Tox. 4, H302 Harmful if swallowed. Eye Irrit. 2, H319 Causes serious eye irritation. (Please see pages 2-3 of submitted comments). ECHA note – An attachment was submitted with the comment above. Refer to non-confidential attachment No. 1 (at the bottom of this document).				

Dossier Submitter's Response
In line with the instructions in the Guidance on the preparation of dossiers for harmonised classification and labelling (version 2.0, August 2014), the hazard classes skin and eye irritation were not included in the CLH dossier as no change to the current classification was proposed*. While we agree that it would be more transparent to always address all hazard classes for active substances in BP and PPP in the CLH dossiers, regardless of whether or not a change is proposed, these hazard classes are not open for commenting thus we cannot discuss the argumentation presented in the attachment at this stage of the process. *"*For active substances in the meaning of the BP and PPP legislations, CLH dossiers should normally address all hazard classes and differentiations unless there is already an existing entry in Annex VI to CLP (see Section 3.4.3 and 5.4.1.1).*"
RAC's response
Thank you for your comment. RAC agrees with the DS that it is not possible to change the classification of hazard classes that have not been discussed in the dossier.

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United Kingdom	SC Johnson	Company-Manufacturer	4
Comment received				
The CLH report on the harmonised classification and labelling of DEET proposes updates to the harmonised classification of DEET, a common insect repellent active ingredient. As a manufacturer of DEET-based personal insect repellents, SC Johnson appreciates the opportunity to comment on the report, specifically in regard to the specific target organ toxicity and the skin irritation hazard endpoints. These comments are provided in the attached PDF. ECHA note – An attachment was submitted with the comment above. Refer to non-confidential attachment No. 2 (at the bottom of this document).				
Dossier Submitter's Response				
Please note our response to comment 3.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2016	Belgium		Member State	5
Comment received				
First of all, data quality and adequacy is difficult to evaluate considering that the reliabilities are missing for this endpoint and some more detailed data should have been included (A6.5.(2) and A6.7(1): how can we explain the low survival rate? Was this observed in all (treated) groups? Though the conclusion is "not considered carcinogenic", what are the numerical data? the lack of numerical data is also valid for study A6.7(2) concerning the conclusion about the "small" changes in body and liver weights).				

No evidence of carcinogenic effect on rats or mice can be highlighted given the available data.
Dossier Submitter's Response
We apologize if the presentation of results in the CLH report was unsatisfactory. More detailed information on the findings of the study (as well as the other studies discussed in the CLH report) is available in the robust study summaries included as an attachment in IUCLID. This approach was a compromise between the extensive confidentiality claims made by the applicant for the biocides review (providing the majority of studies) and the necessity for Member States and members of RAC to make an independent and transparent review of data. With respect to the low survival rate and its impact on the reliability of the study, please note our response to comment number 6.
RAC's response
Thank you for your comment. RAC agrees that the available evidence is insufficient to propose a classification for carcinogenicity. See also the response to Comment 6.

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	France		Member State	6
Comment received				
Please specify the reliability of the studies presented in table 19 (p31). Reasons for the high mortality found in the carcinogenicity study in rats are not specified in the CLH report. Please explain and add a statement regarding the potential impact on the reliability of this study. Testicular effects have been observed in different experimental studies, thus it would be appreciable to have more details on results and limitations of the study on Swedish workers presented in section 4.9.3.				
Dossier Submitter's Response				
The survival rate in high, mid and low dose males and in control 1/control 2 males are 23, 22, 24 and 31/29 (of a total number of 60 animals/group). The corresponding numbers in females are 23, 28, 16 and 17/23 in high, mid and low dose females and in control 1/control 2 females. The low survival rate was not further explained in the report. Considering that figures are fairly comparable between groups and that there is no apparent dose-response, the reduced survival does not seems to result from the use of too high doses. The macro and microscopic analyses made did not indicate treatment-related neoplastic findings in animals (terminally sacrificed, decedents and animals killed in extremis). However, the reduced survival rate impacts on the statistical power of the study and it is not possible to exclude that the tumour incidence could have been different if a higher number of animals survived to termination. Therefore, the reliability of this study is downgraded to 2-3 meaning that the results should be interpreted with some caution. The survival rate in the 18 month study in mice was >50% in all groups and there were no other deviations considered to compromise the study. Therefore, the reliability of this study is 1. With respect to testicular effects it is noted that a slight increase of leydig cell tumours were observed in rats surviving to termination (2/23, or 8.7%) compared to 0 in control 1 and control 2 groups). The frequency of this tumour type was not increased in mice. The results from the two carcinogenicity studies in rats and mice, are not considered to meet criteria for classification with respect to carcinogenicity. Nevertheless, it is				

recognized that the reduced survival rate in the rat study brings some uncertainty to the reliability of results.

Testicular effects are indeed noted in some animal studies but findings seem inconsistent between species and/or studies (see study summaries in Doc IIIA). In hamsters, effects such as reduced testis weight, histopathological signs of tubular degeneration of testis (bilateral), luminar debris of epididymidis) are observed at doses above 300 mg/kg bw. There were no testicular effects in the rat studies but high dose testing was limited by kidney toxicity. However, in the 90 day oral study the relative testis weight was increased (without histopathological findings) at a dose of 1000 mg/kg bw/day. Reduced testis weight (without histopathological findings) was observed in an 8 week dog study at 400 mg/kg bw but no such effects were noted at the same level in the one year dog study.

The study on Swedish workers is a case-control study which is based on self-administered questionnaires investigating 26 occupations and 29 different agents as potential risk factors for testicular cancer. The results from 39 cases and 54 controls showed an odds ratio of 1.7 for insect repellents. According to the publication, *"the majority of insect repellents in Sweden contain N, N-diethyl-m-toluamide (DEET) as the active ingredient"* but it is not clearly stated that workers were exposed to DEET. Therefore, this information should be interpreted with some caution.
Overall, the results from the carcinogenicity studies in rats and mice and the concern indicated in the published case-control study are not considered to demonstrate that criteria for classification are fulfilled.
Hardell L, Nasman A, Ohlson CG, et al. 1998. Case-control study on risk factors for testicular cancer. Int J Oncol 13(6):1299-1303.

RAC's response

Thank you for your comment. The additional information provided by the DS has been included in the assessment by RAC. Considering the uncertainties in the rat study and the case-control study on Swedish workers, the RAC agrees with the DS that the available evidence is insufficient to propose a classification for carcinogenicity.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2016	Belgium		Member State	7

Comment received

Four in vitro studies presented in Table 18 with acceptable reliabilities were negative; however, another study is mentioned (Page 29, Tisch et al., 2002) where possible genotoxic effects have been observed. It would have been interesting to give more details about this last study and include it in Table 18. Further investigation may be needed to conclude on this endpoint, even if the mutagenic potential of DEET is probably low.

Dossier Submitter's Response

As discussed in the CLH report, the results in the study by Tisch et al indicate that further studies on the genotoxic potential may be needed. Further details on this particular study is not considered to add to the decision on classification. The study is an in vitro study in nasal mucosal cells and the result, even if truly positive, would not be sufficient to fulfil criteria taking into account the negative results obtained in the three in vitro guideline studies and the lack of reliable in vivo data. Nevertheless, as requested, some additional information about the results are shown in the table below.

Authors note that cells from the middle turbinate were more sensitive possibly due to differences in the intracellular metabolism of this agent, DNA repair capacity or antioxidant defences.

	Solvent control	DEET 0.5 mM	DEET 0.75 mM	DEET 1.0 mM
Middle turbinate % undamaged cells	89.6±5.7	51.4±4.6	36.3±3.4	20.4±5.2
Inferior turbinate % undamaged cells	92.4±4.6	65.4±6.2	48.3±5.5	28.3±6.3
There were no significant cytotoxic effects according to the cell viability test (trypan blue exclusion test) shed.				

RAC's response

Thank you for your comment. The additional information provided by the DS has been included in the assessment by RAC. The RAC agrees that the study by Tisch et al. and the dominant lethal assay presented under Comment 8 support the need for further investigation on mutagenicity. However, the current evidence is insufficient to conclude on this endpoint.

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	France		Member State	8

Comment received

We agree with the classification proposal. However, it would be appreciable to give more details on positive studies (Comet assay and dominant lethal assay).

Dossier Submitter's Response

Further information on the *in vitro* Comet assay is available in our response to comment number 7.
The following information on the DL study is available in the document referred to:

"In a dominant lethal assay, 10 male ICR/Ha Swiss mice received a single dose of DEET (95% meta, remainder other isomers) at 600 mg/kg (Swentzel, 1978). Ten mice/group in the positive and concurrent control groups received 10 mg/kg of TEM and 5 mg/kg corn oil, respectively. The males were then cohoused sequentially with 3 untreated virgin female mice 5 days/week for 8 weeks. Females were sacrificed 13 days after the midweek of their cohabitation with a male. Although the fertility index was not significantly different from the concurrent controls, the total percentage of dams with less than 8 implantations over 8 weeks was greater in the males exposed to DEET than in the control animals (11.6% vs. 3.1%). This study had several deficiencies including only one dose level, too few pregnant females per group, and no individual data."

RAC's response

Thank you for your comment. See the response to Comment 7.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2016	Belgium		Member State	9

Comment received

There is no evidence of reproductive toxicity according to the available data. Some numerical data table would have been appreciated.

Indeed, neurotoxicity evaluation of DEET is a borderline case:
- Acute studies: neurological symptoms were noted in14 human cases after dermal exposure and seizures were observed in children (poison control centers data and in

Scoenig and Osimitz, 2001)
- STOT SE studies: neurological effects were seen in dogs where abnormal head movements were noted in studies A6.3.1(1) and (2). Furthermore, ataxia, tremors and/or convulsions were also noted in study A6.5(1). Several symptoms were reported in rats such as increase response time to heat stimulus in A6.9(1) and transient increase in locomotor activity in A6.8(2). These clinical signs were reported on a weekly basis and were not linked to histopathological findings.
- DEET induces neuroexcitation and is able to block Na+ and K+ channels (Swales et al., 2014) which "could explain a numbness feeling in the mouth or the lips after incautious application of DEET".
Thus, neurotoxic effects were observed in acute studies and in pre-treatment studies where it is unfortunately difficult to know if the symptoms appeared after a single or repeated dose, plus, there is no indication of increase of the severity over time. However, as humans and dogs (rat studies were of poor reliability) nervous systems seem to be sensitive to DEET, a deeper neurological assessment would be greatly interesting.

Dossier Submitter's Response

More detailed information on the findings in the reproductive toxicity studies (as well as the other studies discussed in the CLH report) is available in the robust study summaries included as an attachment in IUCLID. This approach was a compromise between the extensive confidentiality claims made by the applicant for the biocides review (providing the majority of studies) and the necessity for Member States and members of RAC to make an independent and transparent review of data. We apologize for any inconveniences this approach may bring.

We agree that it is difficult to conclude whether or not STOT-SE is warranted hence the hazard class was addressed despite that no classification was proposed.
The decision not to propose classification was taken after a careful comparison of the information available with the criteria for STOT-SE.
As stated in the report, we find it difficult to exclude that the neurological signs in dogs result from a concomitant high general toxicity rather from a specific effect on the nervous system. Considering that this substance is extensively used by humans and yet the case reports available cannot demonstrate a clear link between the signs of neurotoxicity observed and treatment (due to underlying/concomitant disease, misuse etc.), our interpretation is that criteria are not fulfilled.

RAC's response

Thank you for your comment. RAC agrees that classification for reproductive toxicity is not warranted.
The endpoint STOT SE is discussed under Comment 17.

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	France		Member State	10

Comment received

Considering the deficiencies from current guideline, the reliability of 1 is considered not appropriate for the study A6.8.2.

Dossier Submitter's Response

We agree that the reliability of the study is compromised by the deviations from guidelines. Nevertheless, since there were no effects on the ability to reproduce, the lack

of investigations on sperm parameters, oestrous cycle etc. is not considered to invalidate the results of the study.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2016	Belgium		Member State	11
Comment received				
We agree to classify DEET as Acute Tox. 4 (H302) since the oral LD50 is 1892 mg/kg, which is < 2000 mg/kg, thus criteria are correctly fulfilled.				
Dossier Submitter's Response				
Thank you for informing about your position.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United States	DEET EU Joint Venture (DEET EUJV)	Industry or trade association	12
Comment received				
Acute toxicity: oral The oral LD50 is 1892 mg/kg and DEET thus meets criteria for classification in category 4, i.e. oral LD50 >300 but ≤ 2000 mg/kg bodyweight. The DEET EUJV agrees with this interpretation of the pertinent data and proposed classification Acute Tox. 4, H302. (Please see page 2 of submitted comments). ECHA note – An attachment was submitted with the comment above. Refer to non-confidential attachment No. 1 (at the bottom of this document).				
Dossier Submitter's Response				
Thank you for informing about your position.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United States	DEET EU Joint Venture (DEET EUJV)	Industry or trade association	13
Comment received				
Hazard class is not assessed in the final CLH report; however, the DEET EUJV strongly disagrees with the interpretation of the pertinent data and proposed classification Skin Irrit. 2, H315. Primary dermal irritation has been evaluated for the active substance, DEET. The result of this GLP primary skin irritation study conducted to a stringent regulatory testing guideline was "slightly irritating" but clearly reversible, which did not trigger classification by CLP				

guidance criteria. In addition, human dermal clinical study results, published medical data and the long history of safe consumer use consisting of billions of applications, support the conclusion that skin irritation is an exceedingly rare event in association with the normal and intended use of DEET insect repellent products.
A detailed review of the dermal irritation assessment referred to in the Competent Authority Report of KEMI is enclosed in the Annex below. (Please see pages 2 and 4-8 of submitted comments).

ECHA note – An attachment was submitted with the comment above. Refer to non-confidential attachment No. 1 (at the bottom of this document).

Dossier Submitter's Response

In line with the instructions in in the Guidance on the preparation of dossiers for harmonised classification and labelling (version 2.0, August 2014), the hazard classes skin and eye irritation were not included in the CLH dossier as no change to the current classification was proposed*.
While we agree that it would be more transparent to always address all hazard classes for active substances in BP and PPP in the CLH dossiers, regardless of whether or not a change is proposed, these hazard classes are not open for commenting thus we cannot discuss the argumentation presented in the attachment at this stage of the process.

*"For active substances in the meaning of the BP and PPP legislations, CLH dossiers should normally address all hazard classes and differentiations unless there is already an existing entry in Annex VI to CLP (see Section 3.4.3 and 5.4.1.1)."

RAC's response

Thank you for your comment. RAC agrees with the DS that at this stage it is not possible to change the classification of any hazard classes that have not been discussed in the dossier.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United States	DEET EU Joint Venture (DEET EUJV)	Industry or trade association	14

Comment received

Although this hazard class is not assessed in the final CLH report, the DEET EUJV agrees with the interpretation of the pertinent data and proposed classification Eye Irrit. 2, H319. (Please see page 2 of submitted comments).

ECHA note – An attachment was submitted with the comment above. Refer to non-confidential attachment No. 1 (at the bottom of this document).

Dossier Submitter's Response

Please note the response to comment 13.

RAC's response

Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2016	Belgium		Member State	15
Comment received				
It is difficult to conclude on that endpoint, considering the low amount of data generated after a single exposure to DEET and the clear impact of DEET on the nervous system of dogs.				
Dossier Submitter's Response				
We agree that it is difficult to conclude whether or not STOT-SE is warranted hence the hazard class was addressed despite that no classification was proposed. The decision not to propose classification was taken after a careful comparison of the information available with the criteria for STOT-SE. As stated in the report, we find it difficult to exclude that the neurological signs in dogs result from a concomitant high general toxicity rather from a specific effect on the nervous system. Considering that this substance is extensively used by humans and yet the case reports available cannot demonstrate a clear link between the signs of neurotoxicity observed and treatment, our interpretation is that criteria are not fulfilled.				
RAC's response				
Thank you for your comment. See the response to comment 17.				

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United States	DEET EU Joint Venture (DEET EUJV)	Industry or trade association	16
Comment received				
This hazard class is discussed extensively in the CLH report, although no classification is proposed. KEMI has presented a reasoned and thoughtfully considered case that the acute clinical signs of neurotoxicity observed in dogs treated by bolus oral administration with DEET may occur near doses that are lethal to dogs. In the very robust and extensive safety database developed by the DEET Joint Venture for regulatory registrations of DEET, no acute neurotoxic effects were observed in studies with the other mammalian species. An overall conclusion was made by KEMI that acute effects in dogs dosed orally do not form conclusive evidence that criteria for STOT-SE classification are fulfilled and, therefore, no classification was proposed in the final CLH report. The DEET EUJV agrees with this interpretation of all the pertinent data and proposed non-classification for this hazard class. (Please see page 2 of submitted comments). ECHA note – An attachment was submitted with the comment above. Refer to non-confidential attachment No. 1 (at the bottom of this document).				
Dossier Submitter's Response				
Thank you for informing about your position.				
RAC's response				
Thank you for your comment. See the response to comment 17.				

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	France		Member State	17

Comment received

We agree that dogs are more sensitive to neurotoxicity of DEET compared to rats. No information (ex. ADME data) is provided to conclude that rat is more relevant than dog for extrapolation to human.

In addition, neurotoxicity is found in several human cases; limitations given are not sufficient to disregard the causality of DEET on neurotoxicity effects observed in humans.

Several published data on neurotoxicity are available but not taken into account in this report. This should be considered for classification proposal. (ex. : Briassoulis G et al., 2001; Abdel-Rahman A et al., 2004; Abou-Donia MB et al., 2001…)

Furthermore, the dose of 225 mg/kg bw/day from the subacute study could not be considered as a lethal dose in our view since dogs were exposed to 400 mg/kg bw/day for 1 year without any mortality reported. The relevance of comparing LD50 from rat study to LOAEL from dog study is questionable, without any further information of toxicokinetics in both species.

Thus, we are of the opinion that neurotoxicity is not covered by classification as Acute Tox. 4. Regarding the weight of evidence including dog studies, human cases and mechanistic studies, we are of the opinion that STOT SE 1 should be discussed at the RAC level.

Dossier Submitter's Response

As stated in the CLH report, we think this is a borderline case and we agree that STOT SE 1 should be discussed. Please also note our response to comment 15.
To clarify, we do not state that 225 mg/kg bw is a lethal dose in dogs but we state that, based on the decision to terminate this group due to clinical signs, this dose may be close to lethal doses and thus overlap with the classification proposed for acute oral toxicity, i.e. classification in category 4 (i.e. 300 mg/kg bw >ATE ≤ 2000 mg/kg bw/d).

We are aware of the extensive amount of literature available and we have tried to skim through this to an extent considered reasonable. Of course we may have overlooked important information. However, the publications referred to above, i.e. studies by Abou-Donia et al. and Abdel-Rahman et al., are relevant but seem to have some major deficiencies in reliability. Unfortunately there are no similar dermal studies performed according to principles of GLP and recognized guideline. While the concern raised from these types of publications can be taken into consideration in a risk assessment (by being precautious in the choice of assessment factor, margin of exposure, etc.) our interpretation of criteria is that the information available do not meet criteria for classification STOT-SE.

RAC's response

Thank you for your comment. Classification for STOT SE based on the neurotoxic effects in dogs and human cases has been discussed at the RAC meeting. It was concluded that, in view of the small number of cases reported in humans (relative to the extensive use of the substance), limitations in the data from dogs (including small number of animals, relatively low incidence of severe effects, and absence of histopathological correlate) and

insufficient effects in other species, RAC agrees with the proposal by the dossier submitter for no classification for STOT SE.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2016	Belgium		Member State	18

Comment received

No overview table is given of ALL available aquatic toxicity studies with DEET.
- Were the studies reported in the CLH dossier performed GLP? Were validity criteria met? Besides deviations reported for acute Daphnia study, do the reported studies deviate from the test guideline?
- What is the outcome from the other studies not mentioned in the CLH report, what about their reliability, validity, do they deviate from the test guidelines ?
Furthermore, where large data sets are available (n ≥4) for the same species, geometric mean of toxicity values may be used as the representative toxicity value for that species.

In case of very large datasets Species Sensitivity Distribution may be considered.
Ready biodegradation: Were validity criteria for the 3 reported tests met? What is the origin and cell density of the inoculum? Were toxicity controls conducted?
- Kumar (2003a): Out of the 6 OECD ready degradation studies, the lowest test substance concentration (2-10 mg/l) is used in the OECD 301D. Inhibition of respiration of microorganism resulted in a 3hEC50>1000mg/l. Combined with the 87% ThOD/95%COD for the reference substance, it seems unlikely that halted degradation is due to toxicity of the micro-organisms.
- OECD301 C: an acute toxicity study is mentioned with phosphorent bacteria (Kaiser and Palabrica in Weeks et al 2011) showing toxicity. However, no value is reported in the CLH report.
If the positive result (degradation higher than the pass level) in the OECD 301B study is of good scientific quality and if test conditions are well documented, the substance can be considered as ready biodegradable in a weight of evidence approach.

Adsorption/desorption
Another study following OECD 106 "Adsorption-desorption using a batch equilibrium" is available, resulting in Koc between 47-126L/kg (Weeks et al, 2012) indicating low to moderate mobility.

Dossier Submitter's Response

We did explain in the CHL report under section "5.4 Aquatic toxicity" that there is a large dataset on the acute and long-term toxicity of aquatic organisms and the most relevant studies and endpoints have been selected for the evaluation and environmental CHL proposal of DEET.

For the degradation studies for DEET, there is a description in the CHL report of the key study on the ready biodegradability study according to the OECD guideline 301 B. Since this a standardized degradation test, highly recommended for classification purposes of ready biodegradability and the test was reliable, we decided to use it as a key study. The other degradation studies with lower reliability and with contradicting results on the degradation, we did give information and a discussion in the CHL report and the reason why we did not use them as key studies. The acute toxicity study with the luminescent bacteria reported an EC50 of 68 mg/L which might indicate a toxicity of microbes (Kaiser and Palabrica 1991). This study was only used to explain one of the reasons why we did not choose the OECD 301 C as a ready biodegradable test for the classification purpose of

DEET and therefor was not described in detail. We agree this test result is in contradiction with OECD 209 study where DEET was demonstrated to have low toxicity to micro-organisms (EC50 > 1000 mg/l).Nerveless there seem to be an effect on some microbes as in the study of Kaiser and Palabrica 1991 showed.

For the adsorption/desorption test we decided to take the information from the A.3.2 in Final CAR March 2010. The information on adsorption/desorption test from Weeks et. al 2011 is of interest but would not effect the outcome of the classification proposal.

RAC's response

Please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2016	Finland		Member State	19

Comment received

In principle we support the removal of environmental classification for N,N-Diethyl-meta-Toluamide (DEET) which is based on the conclusion that DEET should be considered as a readily biodegradable substance and aquatic ecotoxicity studies show a low toxicity. In our opinion more information should be given to make a definite decision.

Regarding biodegradability it is noted that both positive (OECD 301 B) and negative (OECD 301 C) results are presented in the CLH dossier. As said in the CLP guidance where conflicting datasets exist the most reliable data should be used and positive results could be considered valid, irrespective of negative results, when the scientific quality is good and the test conditions are well documented.

According to the Dossier submitter the 301 B study showing biodegradability of 83.8% (reached within 28 d and the 10d window) is the most reliable as there is no deviation from the guideline and validity criteria in the OECD guideline is fulfilled. On the other hand the OECD 301 C study, where no biodegradation was observed, was said to be less reliable because it was unsure whether test substance (in the test concentration of 100 mg/l) was toxic to microbes. Reference to support that speculation was made to Kaiser and Palabrica in Weeks et al 2011 where acute toxicity to phosphorent bacteria was shown.

Keeping the CLP guidance in mind we still hesitate whether information provided in the CLH dossier is strong enough for removal of current environmental classification. Instead of not assigning any environmental classification would the Aquatic Chronic Category 4 classification be warranted? To make a decision both studies 301 B and 301 C (e.g. was toxicity control included?) should be described more in detail to confirm the conclusion on biodegradability. In addition more information on Kaiser and Palabrica in Weeks et al 2011 study should be presented i.e. in which concentration DEET was found to be toxic as there seems to be a contradiction to OECD 209 study where DEET was demonstrated to have low toxicity to micro-organisms (EC50 > 1000 mg/l).

Dossier Submitter's Response

For the degradation studies for DEET there is a description in the CHL report of of the key study with the ready biodegradability study according to the OECD guideline 301 B. Since this a standardized degradation test, highly recommended for classification purposes of ready biodegradability and the test was reliable we decided to use it as a key study.

The other degradation studies with lower reliability and with contradicting results on the degradation, we did give information and a discussion in the CHL report why we did not use them as key studies. The acute toxicity study with the luminencent bacteria reported an EC50 of 68 mg/L which might indicate a toxicity of microbes (Kaiser and Palabrica 1991). This study was only used one of the arguments to explain why we not choose the OECD 301 C as a ready biodegradable test for the classification purpose of DEET and therefor was not described in detail. We agree this test result is in contradiction with OECD 209 study where DEET was demonstrated to have low toxicity to micro-organisms (EC50 > 1000 mg/l).Neverless there seem to be an effect on some microbes as in the study of Kaiser and Palabrica, 1991 showed.

We have already discussed in the CHL report of the classification proposal of DEET why we did not choose the modified older MITI test (reliable with restriction classified in Weeks,2011) conducted and based on OECD guideline 301 C as a key study and instead choosed the more standardized and new ready biodegradable test(high reliability classified in Weeks 2011) according to OECD guideline 301 B.

RAC's response

Please see the RAC opinion. RAC did not feel that Aquatic Chronic Category 4 is needed in this case. The data gap was chronic fish toxicity which could, in RAC's view, be clarified with QSAR calculations.

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United Kingdom		Member State	20

Comment received

Given the chronic toxicity to Daphnia magna study was not included in the CAR and reviewed under Directive 98/8/EEC, we feel further information to clarify study validity and endpoints should be presented for CLH. For example, was the study run to GLP, were there any study deviations, are the endpoints based on mean measured or nominal concentrations, and were study validity criteria met. This is important as the study exhibits the lowest chronic NOEC (21d NOEC 3.7 mg/l for length).

Dossier Submitter's Response

Since the chronic toxicity study with Daphnia magna was a published article and a reliable and supportive study that followed a standardized guideline, we decided not to give a more detailed information on this study.

RAC's response

RAC agrees with the commenting MS but accepts the result based on the DS statement realizing that this causes some uncertainty to the classification. Using the surrogate system (acute toxicity, rapid biodegradability and bioaccumulation potential) the outcome would lead to the same classification conclusion.

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	United States	DEET EU Joint Venture (DEET EUJV)	Industry or trade association	21

Comment received

DEET is rapidly biodegradable, based on the most reliable ready biodegradation study (OECD 301 B testing guideline) result of 83.8% biodegradation. This result achieved the

criteria of >70% CO2 evolution in a 10-day window after passing 10% degradation within the 28-day period of the test. Also, DEET does not fulfill the criterion for bioaccumulation based on its log Ko/w < 4 and its BCF < 500. The criterion for chronic toxicity (NOEC<1 mg/L) is not fulfilled based on the long term reproduction study with Daphnia 21-day NOEC= 14 mg/L and the most reliable acute toxicity studies for both fish and algae with NOECs >1 mg/L. It is proposed in the final CLH report that DEET should not be assigned any classification for environment and, therefore, DEET is proposed to be declassified in relation to the current environmental classification. The DEET EUJV agrees with this interpretation of the pertinent data and proposed declassification for aquatic toxicity from Aquatic Chronic 3, H412 to not classified. (Please see pages 1-2 of submitted comments). ECHA note – An attachment was submitted with the comment above. Refer to non-confidential attachment No. 1 (at the bottom of this document).
Dossier Submitter's Response
Noted.
RAC's response
Please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
12.08.2016	France		Member State	22
Comment received				
We agree with the current proposal for consideration by RAC: DEET should not be assigned any classification for environment. Thus, DEET should be declassified in relation to the current environmental classification.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Please see the RAC opinion.				

NON-CONFIDENTIAL ATTACHMENTS

1. *FINAL DEET EUJV CLH Comments_11Aug2015.pdf*. Submitted on 12/08/2016 by DEET EU Joint Venture (DEET EUJV). [Please refer to comments No. 3, 12, 13, 14, 16, 21]
2. *SCJ comments to DEET CLH report.pdf*. Submitted on 12/08/2016 by SC Johnson. [Please refer to comment No. 4]