

11 August 2016

DEET EUJV Comments on CLH report:

**Proposal for Harmonised Classification and Labelling
Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2**

Substance Name: N,N-Diethyl-meta-Toluamide (DEET)

EC Number: 205-149-7

CAS Number: 134-62-3

Index Number: 616-018-00-2

Introduction

N,N-Diethyl-meta-toluamide (DEET; CAS No. 134-62-3; EC No. 205-149-7) is an active substance that is used worldwide in many topically applied insect repellent products. It repels biting pests such as mosquitoes and ticks, most importantly including species that may carry malaria, Dengue fever, West Nile virus, Zika virus, Lyme disease, encephalitis and other diseases.

The DEET EU Joint Venture (EUJV) is a consortium of DEET manufacturers operating under the auspices of the Consumer Specialty Products Association, formed to jointly develop and submit required data pursuant to European Biocidal Products Regulations. The DEET EUJV members Clariant and Vertellus are in close cooperation with SC Johnson and supported by the consultant Toxicology Regulatory Services.

Sweden was designated as Rapporteur Member State (RMS) to carry out the Biocidal Products Directive (BPD) assessment of DEET. The Swedish Chemicals Agency (KEMI) prepared the final Competent Authority Report (CAR) in 2010 and has proposed updates to the harmonised classification of DEET based on the criteria of the CLP Regulation 1272/2008. The proposed change from the current entry in Annex VI, CLP Regulation is to remove the Aquatic Chronic 3, H412 classification, resulting in the following proposed harmonised classification:

Acute Tox. 4, H302	Harmful if swallowed.
Eye Irrit. 2, H319	Causes serious eye irritation.
Skin Irrit. 2, H315	Causes skin irritation.

Herein the DEET EUJV comments on the harmonised classification proposal, in order to establish the most appropriate classification of DEET, based on the toxicological data available and the criteria of the CLP Regulation.

Comments on the proposed classification and the CLH report

Aquatic toxicity

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 K_{ow} < 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.

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.

Eye irritation

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.

Skin irritation

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.

Specific target organ toxicity – single exposure (STOT SE)

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.

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.

DEET EUJV proposed 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.

Conclusion

In conclusion, the very high dose levels of undiluted DEET employed and 90 consecutive days of dermal exposure without removal of the test substance in micropig[®] and rat subchronic toxicity studies, makes these studies inappropriate for assessment of dermal irritation hazard. This conclusion is supported by the “slightly irritating” result of the standardized regulatory guideline rabbit primary dermal irritation study (CAR Doc III A6.1.4(1)) specifically designed to assess the hazard of this endpoint with a single 4-hour exposure, which does not trigger Skin irritation 2, H315 classification. More importantly, the extensive and well-documented consumer experience demonstrates that the occurrence rate of possible cases of skin irritation associated with use of DEET products is on the order of 1 per 100 million applications.

Annex

Skin irritation

Primary dermal irritation has been evaluated for the active substance, DEET (CAR Doc IIA; CAR Doc III A6.1.4(1)). Using a standardized, regulatory guideline rabbit skin irritation study (EPA OPPTS 870.2500) New Zealand albino rabbits were exposed to a semi-occlusive dose of undiluted DEET (98.33% purity) for 4 hours at a dose volume of 0.5 mL (approximately 200 mg/kg bw for 2.5 kg bw rabbits) and surface area ~6 cm². Average irritation scores for 1, 24, 48, 72 hours and 7 days were: Erythema 1.7, 1.3, 1.0, 0.3, 0.0 and Edema 0.3, 1.0, 1.0, 0.0, 0.0. 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.

Nonetheless, in CAR Doc IIA, 3.3 the following rationale was given by the RMS as the basis for classification of the active substance, DEET:

“DEET is ‘slightly irritating’ to the skin. However, 90-day repeated dose studies (dermal) in pigs and rats showed that repeated dermal dosing resulted in dermal irritation at all doses (≥ 100 mg/kg/bw/day) tested and remained at study end. Dermal irritation was expressed as red application area, dry skin, acanthosis and/or hyperkeratinosis, scabbing, dermal scaling. In rats also hair loss occurred. In the human exposure study at 95th percentile of use (50 mg/kg bw/day), no dermal irritation was observed when undiluted DEET was applied to skin (metabolism study, CAR III-A6.2(4)), but it should be noted that the number of test subjects were low, i.e. 3/sex, and there were only four daily 8-hour dermal applications.”

However, no substantiating documentation is provided in the CAR that indicates a methodical analysis of the micropig[®] and rat data underlying the classification of DEET by the RMS was conducted. Only qualitative observations were used as rationale in the statement above. More careful review of the details of the robust summary for Subchronic dermal toxicity test in non-rodents (micropig[®]) reveals the information below (CAR Doc III A6.4.2(1)). These results do not support a conclusion that DEET is irritating to the skin when used as an insect repellent according to standard criteria because skin effects in the dermal subchronic toxicity study were only observed after weeks of repeated 24-hour exposures at dermal dose levels as high as 1000 mg/kg bw/day, whereas the dosing regimen for the standard primary dermal irritation study is a single 4-hour application of about 200 mg/kg bw:

Results: Only two cases of slight erythema at 100 mg/kg bw/day (week 5), one case of slight erythema at 300 mg/kg bw/day (weeks 5, 6 and 7), zero cases of erythema at 1000 mg/kg bw/day, and no edema or signs of severe irritation effects were observed during the 13-week study. An increased incidence of desquamation of the skin at the site of test substance application was noted in all treatment groups starting at approximately Week 4 and increased in severity through study termination. Increased incidences of dry skin were also noted in the treatment groups beginning around Week 2 and persisting until study termination. These observations were attributed to exposure to the test substance, although they are not indicative of skin irritation. See CAR Doc IIIA, Table A6.4.2 (1)-1. Note: Dose levels were 100, 300, and 1000 mg/kg bw/day and test substance was not removed before the next dose. These test conditions are much more severe than the standardized primary dermal irritation study conducted using New Zealand albino rabbits with a single 4-hour application of about 200 mg/kg bw.

Similarly, review of the details of the robust summary for Subchronic dermal toxicity test in rodents (rats) reveals the information below (CAR Doc III A6.4.2(2)). These results do not support a conclusion that DEET is irritating to the skin when used as an insect repellent according to standard criteria because skin effects in the dermal subchronic toxicity study were only observed after weeks of repeated 24-hour exposures at dermal dose levels as high as 1000 mg/kg bw/day, whereas the dosing regimen for the standard primary dermal irritation study is a single 4-hour application of about 200 mg/kg bw:

Dermal Scores: There was an increased occurrence of red areas at the application site (i.e. not erythema) for the rats in the treated groups in comparison to the control group. The red areas at the test site were observed primarily during Weeks 1-3, but were present later in the study, particularly for the 300 mg/kg/day treated females. Slight erythema (score of 1) was present beginning Week 6 for 3 of 15 females in the 300 mg/kg/day dose group in which red areas also occurred during Weeks 6-14. Erythema was not observed for males at any dose level or in any females in the 0, 100 or 1000 mg/kg/day dose groups. Oedema was not observed at any time in any animals. There was a slight increase in scabbing at the application site in treated rats as compared to the controls, although this is not indicative of skin irritation. The highest incidence of scabbing occurred during the first weeks of the study, but was present through Week 13. See CAR Doc IIIA, Table A6.4.2 (2)-1.

Note: Dose levels were 100, 300, and 1000 mg/kg bw/day and test substance was not removed before the next dose. These test conditions are much more severe than the standardized primary dermal irritation study conducted using New Zealand albino rabbits with a single 4-hour application of about 200 mg/kg bw.

The human data and experience with DEET as an insect repellent active substance are discussed as follows.

In a Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) compliant human volunteer study of pharmacokinetics following dermal application of undiluted DEET, three healthy female and three healthy male subjects were enrolled in the 4-day study (CAR Doc III A6.2(4); Schoenig and Osimitz, 2001¹). All subjects were regular users of products formulated with DEET. Undiluted DEET was applied once per day for four consecutive days at a level of 3 g/day for females and 4 g/day for males or approximately 50 mg/kg bw/day (95th percentile of consumer use rate). Undiluted DEET was applied to both legs and one arm of each subject using glass syringes and spread evenly by a clinical technician wearing a polyethylene glove. DEET was not applied to the arm from which blood was drawn. The amount of DEET applied was sufficient to result in a wet appearance, similar in appearance to that which occurs with normal consumer application of DEET, but not enough that dripping or runoff occurred. The application sites were left uncovered. Subjects engaged in normal activity for 8 hours after the application of DEET and then showered with warm water (27-32°C) and Ivory[®] soap for approximately 4-16 min. Subjects were monitored throughout the confinement for general health or for the development of adverse reactions to the test substances or procedures.

There were no clinical complaints or adverse reactions to treatment with undiluted DEET following exposures at the 95th percentile of consumer use rate for 4 consecutive days. Therefore, it may be concluded that the risk of adverse skin reactions by the use of DEET insect repellent products even at maximum used rates is extremely small.

¹ Schoenig, G. P. and Osimitz, T. G. 2001. DEET In: Krieger, R., ed, Handbook of Pesticide Toxicology, Vol 2. Agents, San Diego: Academic Press, pp. 1439-1459.

Medical data for 1995 until 2001 are available from the National Registry of Human Exposures to DEET (CAR Doc III A6.12; Osimitz et al., 2010²). The DEET Joint Venture contracted Pegasus Research, Inc. to operate the Registry. The purpose of the Registry was to collect detailed information from individuals who used DEET-containing insect repellents and reported serious adverse neurologic or systemic effects, in particular; however, data were also collected on moderate effects including skin irritation. Because of its prospective nature, the Registry allowed for quick and thorough follow up on individual cases to determine exposure circumstances, medical data and whether causality between DEET exposure and symptoms could be established.

Table 4 of Osimitz et al. (2010) shows 58 cases (13 Probably; 36 Possibly; 9 Undetermined) of “Dermal only” effects (i.e. skin irritation) collected in the Registry during the 7 years it was active. Table 5 of the same article shows that reported “Dermal only” symptoms do not follow an age-related trend in years and number of cases, respectively: 0–2 yrs (5); 3–5 yrs (8); 6–12 yrs (7); 13–19 yrs (3); Adult (35); Unknown (0). Similarly, Table 7 of this publication demonstrates the lack of a DEET concentration (%) related trend and number of “Dermal only” cases: 0–10% (16); 10.1–20% (9); 20.1–40% (9); 40.1–60% (0); 60.1–100% (2); Unknown (23). It may be concluded that because only a total of 58 cases were classified as “Dermal only” out of over 5 billion applications of DEET that occurred in the population during the 7 year span of the Registry, the overall risk of clinically significant skin irritation events is infinitesimally small and only may be coincidental. This occurrence rate is about 1 possible case of skin irritation associated with the use of DEET products per 100 million (100,000,000) applications.

In order to provide context to the basis for the DEET EUJV’s disagreement with the proposed Skin irritation 2, H315 harmonised classification of DEET, the following excerpts are taken from ECHA Guidance on the Application of the CLP Criteria, Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (Version 4.1, June 2015). The animal data and extensive human experience with DEET does not trigger Skin irritation 2, H315 according to these criteria, especially when also considering the weight of evidence.

3.2.2.2. Classification criteria

[...]

Table 3.2.2
Skin irritation category

Category	Criteria
Category 2: Irritant	(1) Mean value of $\geq 2,3 - \leq 4,0$ for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Annex I: 3.2.2.8. Comments on responses obtained in skin irritation tests in animals.	
Annex I: 3.2.2.8.1. Animal irritant responses within a test can be quite variable, as they are with corrosion. The major criterion for classification of a substance as irritant to skin, as shown in paragraph	

² Osimitz, T.G., Murphy, J.V., Fell, L.A. and Page, B. 2010. Adverse events associated with the use of insect repellents containing N,N-diethyl-m-toluamide (DEET). *Regulatory Toxicology and Pharmacology*. 56:93–99.

3.2.2.7.1, is the mean value of the scores for either erythema/eschar or oedema calculated in at least 2 of 3 tested animals. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure.

Annex I: 3.2.2.8.2. Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a material shall be considered to be an irritant.

3.2.2.3. Evaluation of hazard information

Annex I: 3.2.2.4.

[...]

Although information might be gained from the evaluation of single parameters within a tier (see paragraph 3.2.2.5), e.g. caustic alkalis with extreme pH shall be considered as skin corrosives, there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters.

Generally, primary emphasis shall be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case-by-case determinations are necessary.

Annex I: 3.2.2.5. A tiered approach to the evaluation of initial information shall be considered, where applicable, recognising that all elements may not be relevant in certain cases.

[...]

3.2.2.3.3. Weight of evidence

Where the criteria cannot be applied directly to available identified information, a weight of evidence determination using expert judgement should be applied in accordance with CLP Article 9(3).

[...]

Annex I: 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. **Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data.** However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data

The DEET primary dermal irritation study results and extensive history of safe consumer use of DEET products of all concentrations do not support a classification of Skin irritation 2, H315 based on the above criteria and weight of evidence reproduced from ECHA Guidance on the Application of the CLP Criteria, Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of

substances and mixtures (Version 4.1, June 2015). The plethora of human experience from the almost six decades of using DEET as an insect repellent active ingredient allows a conclusion that the proposed classification Skin irritation 2, H315 would be a very conservative and scientifically unjustified classification since, as discussed previously in this Annex, skin irritation events in consumers associated with use of DEET insect repellents are exceedingly rare and if they do occur, they are mild and rapidly reversible.

Conclusion

In conclusion, the very high dose levels of undiluted DEET employed and 90 consecutive days of dermal exposure without removal of the test substance in micropig[®] and rat subchronic toxicity studies, makes these studies inappropriate for assessment of dermal irritation hazard. This conclusion is supported by the “slightly irritating” result of the standardized regulatory guideline rabbit primary dermal irritation study (CAR Doc III A6.1.4(1)) specifically designed to assess the hazard of this endpoint with a single 4-hour exposure, which does not trigger Skin irritation 2, H315 classification. More importantly, the extensive and well-documented consumer experience demonstrates that the occurrence rate of possible cases of skin irritation associated with use of DEET products is on the order of 1 per 100 million applications.