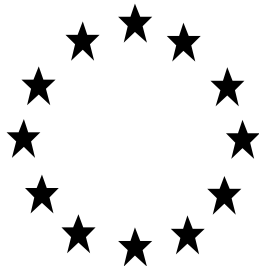
# Directive 98/8/EC concerning the placing biocidal products on the market

***Inclusion of active substances in Annex I or IA to Directive 98/8/EC***

Assessment Report[i]



# N,N- diethyl-*meta*-toluamide (DEET)

# Product-type 19
# (Repellents and attractants)

11 March 2010

Annex I - Sweden

**N,N- diethyl-*meta*-toluamide (DEET) (PT 19)**

**Assessment report**

**Finalised in the Standing Committee on Biocidal Products at its meeting on** Error! Reference source not found. **in view of its inclusion in Annex I or IA to Directive 98/8/EC**

**CONTENTS**

# 1. STATEMENT OF SUBJECT MATTER AND PURPOSE

## 1.1. Procedure followed

This assessment report has been established as a result of the evaluation of N,N-Diethyl-m-toluamide (DEET) as product-type 19 (repellents and attractants), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with a view to the possible inclusion of this substance into Annex I or IA to the Directive.

N,N-Diethyl-*m*-toluamide (DEET), (CAS no. 134-62-3) was notified as an existing active substance, by McKenna, Long and Aldridge LLP on the behalf of DEET EU Joint Venture, hereafter referred to as the applicant, in product-type 19.

Commission Regulation (EC) No 2032/2003 of 4 November 2003[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 5(2) of that Regulation, Sweden was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for N,N-Diethyl-*m*-toluamide (DEET) as an active substance in Product Type 19 was 30 April 2006, in accordance with Annex V of Regulation (EC) No 2032/2003.

On 25th of April, 2006, SE competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on July 25th, 2006.

On 30th November, 2007 the Rapporteur Member State submitted, in accordance with the provisions of Article 10(5) and (7) of Regulation (EC) No 2032/2003, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on January 16th, 2008. The competent authority report included a recommendation for the inclusion of N,N-Diethyl-*m*-toluamide (DEET) in Annex I to the Directive for PT 19.

In accordance with Article 12 of Regulation (EC) No 2032/2003, the Commission made the competent authority report publicly available by electronic means on 16th of January, 2008. This

1 Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

2 Commission Regulation (EC) No 2032/2003 of 4 November 2003 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market and amending Regulation (EC) No 1896/2000. OJ L 307, 24.11.2003, p. 1

report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.

On the basis of the final competent authority report, the Commission proposed the inclusion of N,N-Diethyl-*m*-toluamide (DEET) in Annex I to Directive 98/8/EC and consulted the Standing Committee on Biocidal Product on **Error! Reference source not found.**.

In accordance with Article 11(4) of Regulation (EC) No 2032/2003, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on **Error! Reference source not found.**.

### 1.2. Purpose of the assessment report

This assessment report has been developed and finalised in support of the decision to include N,N-Diethyl-*m*-toluamide (DEET) in Annex I to Directive 98/8/EC for product-type 19. The aim of the assessment report is to facilitate the authorisation in Member States of individual biocidal products in product-type 19 that contain N,N-Diethyl-*m*-toluamide (DEET). In their evaluation, Member States shall apply the provisions of Directive 98/8/EC, in particular the provisions of Article 5 as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available at the Commission website[3], shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Directive 98/8/EC, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

### 1.3. Overall conclusion in the context of Directive 98/8/EC

The overall conclusion from the evaluation is that it may be expected that there are products containing N,N-Diethyl-*m*-toluamide (DEET) for the product-type 19, which will fulfil the requirements laid down in Article 10(1) and (2) of Directive 98/8/EC. This conclusion is however subject to:

i. compliance with the particular requirements in the following sections of this assessment report,

3 http://ec.europa.eu/comm/environment/biocides/index.htm

ii. the implementation of the provisions of Article 5(1) of Directive 98/8/EC, and

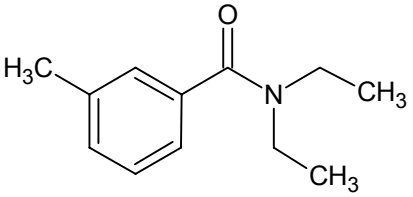
iii. the common principles laid down in Annex VI to Directive 98/8/EC.

Furthermore, these conclusions were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Article 5(1) and of the common principles laid down in Annex VI to Directive 98/8/EC.

## 2. OVERALL SUMMARY AND CONCLUSIONS

### 2.1. Presentation of the Active Substance

#### *2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis*

| | |
|---|---|
| **CAS-No.** | 134-62-3 |
| **EINECS-No.** | 205-149-7 |
| **Other No. (CIPAC, ELINCS)** | Not assigned |
| **IUPAC Name** | N,N-diethyl-m-toluamide |
| **CA Name** | N,N-diethyl-3-methylbenzamide |
| **Common name, synonyms** | Synonyms: DEET |
| **Structural formula** |  |
| **Molecular formula** | $C_{12}H_{17}NO$ |
| **Molecular weight (g/mol)** | 191.27 |
| **Purity of a.s.** | In %w/w:<br>Min 97.8<br>Aim 99.0<br>Max 99.7<br>A minimum purity of 97%w/w is thus proposed |
| **Impurities** | None of the impurities in DEET as manufactured is considered to be relevant.<br>Information on the identity of significant impurities are reported in document III-A2.8. |
| **Additives** | No additives |
| **Representative biocidal product** | OFF!$^{TM}$ Aerosol – 15% DEET (an alcohol based self-pressurized aerosol for direct application containing 15%w/w DEET) |

DEET as manufactured is a clear almost colourless liquid with a mild characteristic DEET odour. Existing data indicates that DEET has a melting point below -20°C and purified DEET has a boiling point of 284.2°C and its relative density is 0.998. The solubility of DEET in water is high (11.2 g/L with no pH control). The pH dependency of the solubility was not assessed,

but DEET is not considered to be able to dissociate at environmentally relevant pH. The vapour pressure was extrapolated to be 0.23 Pa at 25°C, from measurements at 32-52°C and the Henry's Law Constant of 3.93 x 10-3 Pa.m3.mol-1 which indicates that volatilisation is not expected to significantly contribute to the dissipation of DEET in the environment. The Log Pow is 2.4 at pH 6, which indicates no potential for DEET to bioaccumulate. DEET is very soluble in polar as well as in non-polar organic solvents. DEET has a flash-point of 144°C and is not considered to be explosive or oxidizing, based on theoretical considerations. DEET should be regarded as slightly surface active as the surface tension is 58 mN/m at 20°C.

The content of DEET and related impurities in the technical material is determined by GC-FID using external calibration and GC-MS for confirmation of the identities of the analytes. The method has been accurately validated for DEET and all significant impurities. The content of DEET in the representative formulation OFF!TM Aerosol – 15% DEET is determined by HPLC-UV, with external calibration. The method was accurately validated for the aerosol intermediate (i.e. without propellant).

The content of DEET in soil is determined by LC-MS/MS using 1 transition, with a LOQ of 0.01 mg/kg.

No method was considered required for air as the use pattern and the properties of the representative product OFF!TM Aerosol – 15% DEET indicates that the residues of DEET in air will be insignificant. However, a method might be required for different DEET-containing products, and this has to be solved at the product-authorisation stage.

A HPLC-UV method was provided for water, which was validated for data collection in ecotoxicological studies. It has a LOQ of 3 mg/L, which is low enough to cover the effect concentration of the most sensitive aquatic organisms (i.e. 15 mg/l). The method does not comply with requirements for drinking water and no confirmatory method was provided.

At TM I 2009 (March) it was concluded that a monitoring method for the water compartment is needed and that the requirement at a first instance could be addressed with published data. To address this, the applicant submitted three separate published articles describing a LC-MS/MS method for analysis of a broad range of endocrine disruptors and pharmaceuticals, among them DEET, in the natural water compartment. However, the articles do not contain sufficiently detailed validation data to comply with the requirements in the TNsG on Analytical methods and further data in that respect is considered required. The applicant has informed that further validation work is underway that should prove the usefulness of the method for analysing DEET in natural water matrices.

An acceptable HPLC-UV method was provided for the determination of DEET in blood plasma. The method is not highly specific but as DEET is not classified as toxic or highly toxic no further data is required.

No methods are considered required for food or feeding stuffs as the use pattern of DEET and the representative product OFF!TM Aerosol – 15% DEET do not result in any contact with those matrices.

### *2.1.2. Intended Uses and Efficacy*

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II. The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious. Efficacy tests included in section B5 of the CAR, were performed on mosquitoes (aedes aegypti, aedes taeniorhynchus, aedes nigromaculas), stable flies (stomoxys calcitrans), black flies (simulium venustum, simulium nyssa, prosimulium mixtum), deer flies (chrysops atlanticus), ticks (amblyomma americanum) and chiggers (trombicula spp.). Efficacy as an insect repellent has been sufficiently shown in these tests, and more specified testing should be addressed during product authorisation. No efficacy tests were carried out on treated articles or clothing. Furthermore, there is a difference between insect species: the time that the insect is repelled after application of the product (time to first bite) can differ between less then one hour to 6 hours and this has impact on number of applications of the product and should therefore be addressed during product authorisation. It should also be noted that this assessment is based on use of DEET as a repellent and not primarily for use in prevention of insect borne diseases. However repellents containing DEET may be an important tool in the prevention of insect borne diseases such as west Nile Virus but in these situations the use pattern may differ according to perceived risks of contracting disease. In the case of disease prevention the risks of using repellents have to be specifically weighed against the risks of contracting the insect borne disease.

### *2.1.3. Classification and Labelling*

**Current classification of a.s.**

The current harmonised classification and labelling for DEET is according to Annex VI to Regulation (EC) 1272/2008:

Classification in Annex VI, Table 3.2 (in accordance with the criteria in Directive 67/548/EEC):

Xn;R22
Xi;R36/38
R52-53

Labelling in Annex VI, Table 3.2

Xn
R:22-36/38-52/53
S(2-)61

Classification in Annex VI, Table 3.1 (in accordance with the criteria in Regulation (EC) 1272/2008)

Acute Tox. 4 (LD50 is confirmed to be in the range for Acute Tox. 4)
Eye Irrit. 2
Skin Irrit. 2
Aquatic Chronic 3
H302
H319
H315
H412

Labelling

GHS07
Wng
H302
H319
H315
H412

**Proposed classification of a.s.**

During the evaluation of DEET conflicting data regarding biodegradability were available (see Doc II-A 4.1.1.1). Since a reliable study carried out in accordance with OECD TG 301B showing ready biodegradability was submitted (Doc IIIA 7.1.1.2.1), the Technical Meeting I 2009 agreed that DEET can be considered as ready biodegradable. Therefore the current classification needs to be adapted accordingly (i.e. in an Annex XV dossier to be submitted to the ECHA). Conflicting data regarding classification as skin and eye irritant was also found (see doc III-A6.4.1(1), III-A6.4.2(1) and III-A6.4.2(2)), however no change to current classification on irritation is proposed at this stage.

**Current classification of biocidal product OFF™ Aerosol**

Current classification according to the applicant. No changes are proposed by RMS to current classification

F+ Extremely flammable

| | | |
|---|---|---|
| Risk Phrases: | R12 | Extremely flammable |
| (for labelling) | | |
| Safety Phrases: | S2 | Keep out of the reach of children. |
| | S16 | Keep away from sources of ignition – NO SMOKING |
| (for labelling) | | |
| | S23 | Do not breath gas/fumes/vapour/spray |
| | S51 | Use only in well ventilated areas |

Proposed classification and hazard statement according to GHS:

Flam. Aero. 1 H222: Extremely flammable aerosol

Eye irrit. 2, H319 Causes serious eye irritation

The current classification has been directly translated into corresponding GHS phrases, using the translation list "Translation between classification in accordance with Directive 67/548/EEC and the new EU C&L Regulation" i.e Annex VII to Proposal for a Regulation of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, and amending Directive 67/548/EEC and Regulation (EC) No 1907/2006" (COM(2007) 355 final). The product classification therefore needs to be revised during product authorisation.

## 2.2. Summary of the Risk Assessment

### *2.2.1. Human Health Risk Assessment*

#### 2.2.1.1. Hazard identification and effects assessment

The absorption, distribution, metabolism, and excretion studies (ADME) show that, more than 80% of DEET given orally to rats is absorbed and excreted in the urine. DEET showed no evidence for accumulation. When applied dermally to rats 74-78% is absorbed and excreted in the urine. The dermal absorption of DEET occurred at a slower rate than oral absorption (peak plasma concentration ≥4 hr vs.<1 hr, respectively). Seventy-four to ninety-one percent of the administered radioactivity was excreted via urine and about 3-7% was excreted via the faeces. DEET was metabolised completely in all oral and dermal treatment groups with little or no parent compound excreted in the urine. DEET is extensively metabolized to 2 major metabolites, m-[(N,N-diethylamino)carbonyl] benzoic acid and m-[(ethylamino)carbonyl] benzoic acid. DEET is absorbed slowly (peak plasma concentration ≥8 hr), metabolised completely, and excreted rapidly when applied to human skin. Less than 20% (when corrected

for total recovery) of a dermally applied dose of DEET, either as a 15% (w/w) solution in ethanol or as the undiluted technical grade material, is absorbed through the skin during an 8-hour exposure period. Plasma level studies were performed in rats (oral and dermal exposure) and in dogs (oral exposure) to compare plasma levels and area under the curve (AUC) at NOAEL levels with human plasma levels and AUC (dermal exposure).

The acute toxicity studies show that the oral LD50 for DEET warrants a classification as Xn, R22, Harmful if swallowed. The rabbit acute dermal LD50 of DEET is greater than 2000 mg/kg and the rodent acute dermal LD50 is > 5000 mg/kg. The acute inhalation LD50 of DEET is greater than 2.02 mg/L, the highest concentration tested which is lower than the upper EU classification limit, acute toxicity category 4 according to GHS and recommended highest dose according to the OECD guideline. However, in light of animal welfare consideration, testing of animals at higher doses is not considered warranted since inhalation exposure to the product is considered negligible. Even if no mortality was observed at the limit dose tested (2.02 mg/l/4h), it can't be fully ensured that the LC50 would be > 5mg/l/4h. The classification R20 can therefore not be fully ruled out based on this test.

DEET is slightly irritating to the skin. However, repeated dose studies (dermal) in pigs and rats showed that repeated dermal dosing resulted in dermal irritation at all doses tested and remained at study end. A classification as R36, Irritating to eyes is not warranted based on the results in the eye irritation test. However, the mean score for corneal opacity is 1 for three animals at 24, 48 h and 72 h, and warrants a classification as Eye Irrit 2 – H319 according to the GHS.

DEET did not result in a skin sensitisation response in the Buehler test.

Several repeated dose toxicity studies for the oral and dermal route was submitted for DEET. Male rats were the most sensitive gender to DEET for repeated dose effects. Male rats developed alpha2u-globulin nephropathy that is considered gender and species specific. This effect was not considered relevant for risk assessment. Clinical signs of neurotoxicity also occurred in dogs shortly after oral dosing. In both rats and dogs decreased body weights was observed after oral dosing with DEET. Dermal application of DEET to rats and minipigs resulted mainly in skin irritations but no systemic toxicity or pathological findings.

DEET showed no genotoxic potential in a battery of in vitro tests in bacteria and mammalian cells. DEET did not result in an increase in tumours in rats and mice and was not considered oncogenic in the carcinogenicity studies.

The teratogenicity of DEET was investigated in two species, rat and rabbit. The studies were performed according to the OECD 414 guideline and both studies were preceded by dose finding studies. However the studies were performed prior to the latest revision of the OECD guideline in 2001 and has therefore some discrepancies compared to the current guideline. The mothers were treated only during the organogenesis and not to scheduled sacrifice. The studies therefore have some limitations in assessing potential effects during later stages of embryonal development. However considered that the 2-generation study in rats gave no further indications of an embryotoxic or teratogenic effects at comparable doses, these studies are considered acceptable for risk assessment purposes. There were no teratogenic effects observed in the studies up to maternally toxic doses, embryotoxicity was only expressed as decreased foetal body weights (rats).

There were no effects on reproduction in a 2-generation study in rats. Parental males were the most sensitive gender based on kidney effects that were considered species specific and irrelevant for risk assessment to man. There were no effects on reproduction. The effects observed in mothers and offspring were reduced body weights, in offspring during later parts of the lactation period. The study was performed in 1989 and shows therefore some discrepancies compared to the current OECD 416 guideline. The 2-generation study was considered suitable for risk assessment despite deviations from the current OECD 416 guideline.

No studies were submitted by the applicant that specifically investigated neurotoxicity after dermal application. However, neurotoxicity of DEET was investigated in an acute oral delayed neurotoxicity study and in a delayed neurotoxicity study following multigenerational exposure in rats. In the acute neurotoxicity study an increased response time to heat stimulus and decreased rearing activity at one hour post-dose was observed in the high dose group. The multigenerational exposure resulted in a transient increase in locomotor activity in the high dose group. The multigenerational neurotoxicity study has some limitations in assessing the risk on exposure to the developing brain in children since there was no information on exposure to pups during lactation and no functional tests were performed on young animals.

Other studies were submitted to support the conclusion that the kidney effects observed in rats were species specific.

Medical data were collected from various resources, direct observations from clinical cases and published literature. No studies on manufacturing plant personnel were submitted in the dossier. A report was submitted where detailed information was collected in a registry from individuals who used DEET-containing insect repellents and reported local, neurologic or systemic effects. Information on concentrations of DEET products used was available but information was not obtained for application rate. In a 7 year span 12 reports of cases of major (temporary) severity were possibly related to DEET (seizure, other neurological, dermal, and other) and one case of major severity was probably related to DEET (non-neurological). Fifty-nine cases with seizures were reported with 90% of the seizure cases of major or moderate severity. People with underlying seizure disorder were not disproportionately represented (6.8%) in these 59 cases. It was concluded in the report that most of the seizures were probably idiopathic since these are not uncommon, especially in children. Furthermore it was also concluded in the report that because over 5 billion applications of DEET occurred in the population during the 7 year span the overall risk of clinically significant adverse events is extremely low.

Setting of an ADI is not considered necessary, since exposure to DEET is via direct application to skin.

The ARfD of a chemical can be defined as "an estimate of a substance in food and/or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 hours or less, without appreciable health risk to the consumer on the basis of all the known facts at the time of evaluation" (EU guidance, 7199/VI/99/rev 6). By this definition, the setting of ARfD for DEET which is used as an insect repellent directly applied to the skin (PT19) is considered not to be relevant by RMS, since there will be no exposure of DEET via food or drinking water. However since the use of DEET containing repellents include application to the skin on hands and on clothing, there is a risk of ingestion by hand to mouth behaviour, especially in children and an AELacute is proposed to be set. According to the data base on

toxicological effects there is a possibility of acute toxicity manifested as neurotoxicity. The lowest relevant NOAEL for neurotoxicity is based on clinical signs of neurotoxicity. An 8-week oral capsule study in dogs, terminated at day 5 due to severe toxicity, yielded a NOAEL of 75 mg/kg/day based on clinical signs of neurotoxicity (abnormal head movements and ptyalism, emesis, ptosis, ataxia, convulsions). Division by a standard assessment factor of 100, gives an AELacute of 0.75 mg/kg bw/day.

DEET is used as an insect repellent directly applied to the skin. Furthermore, there is according to the applicant currently no production of DEET within the European Union. The setting of an AOEL for professional use, bystanders and re-entry workers is therefore not considered relevant. For risk assessment in consumers an AELrepeated of 8.2 mg/kg bw/day is set based on the 90 day dermal study in rats with a NOAEL of 1000 mg/kg bw/day, the highest achievable dose and using a standard assessment factor of 100 and correction of a dermal absorption of approximately 82% in the rat. It was decided at TM II 2009, to use the dermal study in rats, even though rat was clearly not the most sensitive species with respect to neurotoxic effects. It was discussed to use an additional factor for correcting for the difference in species sensitivity. At the same time it was also discussed that the assessment factor could be reduced due to the availability of human plasma data and plasma data in both rats and dogs, as well as metabolism data in humans and rats. The use of a standard assessment factor of 100 was therefore considered appropriate.

#### 2.2.1.2. Exposure assessment

DEET is intended for use in product-type 19, as an insect repellent directly applied to human skin or clothing at a product concentration of 15% (150 mg/kg). Exposure to DEET is for consumer application, where the intended route of exposure is exclusively dermal. The exposure assessment is based on an application frequency of 2 times per day. Dermal exposure is the main path of exposure but minor contributions to exposure via inhalation of the product during application of repellent spray and via hand to mouth behaviour is theoretically possible. However, the aerosol droplets of the representative product, upon which the risk assessment has been performed, have a mass median aerodynamic diameter (MMAD) of 117 µm and only 10% of particles are <56.8 µm, so DEET reaches the skin as a wet spray. Based on the large MMAD particle size and the rapid sedimentation velocity for particles >100 µm (>25 cm/sec), the sprayed product does not pose an inhalation hazard for humans. Additionally, in "Technical Notes for Guidance - Human Exposure to Biocidal Products - Guidance on Exposure Estimation" (European Commission, 2002, part 2) it is stated in section 5.2 Exposure:

"The inhalation route is excluded due to the use outdoors, and because use indoors only takes place in the summer in situations where there is a high ventilation rate. On these grounds, the inhalation exposure to aerosol sprays is also considered to be negligible."

Oral exposure by hand-to-mouth transfer is not considered to be a significant route of exposure because the smell and taste of DEET acts as a self deterrent against this type of activity. More importantly, the representative product contains an ingredient that acts as a strong deterrent for ingestion (Bitrex). Therefore, the inhalation and oral routes are considered insignificant sources of exposure for the DEET representative product; however calculations for hand to mouth transfer are included by the RMS as worst case exposure calculations to show the importance

of deterrents for ingestion in the products, but are not used in the risk assessment scenarios of the representative product.

The degree of indirect exposure as a result of use of the active substance in this biocidal product is considered negligible, as the primary route of exposure is direct application to the skin. The environmental risk assessment shows that there is little direct transfer occurs of the active substance to the environment during use of this biocidal product.

A user survey study has been performed in the US involving human use and exposure to insect repellents containing DEET. The exposure was calculated by using default values, as proposed by the TNsG and as the 95th and 75th percentile of use, according to the user survey study. The human health exposure scenario for adult consumers at the 75th percentile of use, applying the representative product containing DEET as an insect repellent was used for risk characterization for adults. The 75th percentile was considered acceptable since the user study had a large number of study subjects and the measured exposure was similar to the default exposure value of the TNsG (it should be noted though, that the user survey/usage study presented results from single application/day only). Exposure twice per day was calculated for a body weight of 70 and 60 kg for males and females respectively. A dermal absorption value of 20% was used to calculate internal exposure in humans. Detailed calculations are presented in doc. II. In a similar way the exposure was calculated for children <18 years and <12 years of age (i.e. mean ages of approximately 14 years and 7 years).

#### 2.2.1.3. Risk characterisation

The NOAEL after oral dosing (the daily dose was divided and given as two daily doses a.m and p.m) is 100 mg/kg bw/day, based on the clinical signs of neurotoxicity observed in the 8 week study in dogs and supported by the decreased body weights in the longer term studies. Another 8 week study in dogs where the dose was given as a single daily oral dose was terminated after five days of exposure due to severe clinical signs of neurotoxicity. The critical NOAEL was 75 mg/kg bw/day. The critical NOAEL after dermal dosing in rats is ≥1000 mg/kg bw/day. For primary exposure to the general public an AELacute of 0.75 mg/kg bw/day can be set based on the oral dosing study in dogs (5 days exposure) with a NOAEL of 75 mg/kg bw/day, supported by the 8 week study in dogs and longer term studies in dogs and rats. An AEL repeated of 8.2 mg/kg bw/day is set based on the 90 day dermal studies in rats with a NOAEL of ≥1000 mg/kg/day (the highest dose tested) and a correction for a dermal absorption of approximately 82% in the rat.

The use of the representative product 2 times per day is considered acceptable for adults and children >12 years old i.e the exposure twice per day was 60, 47 and 74% of the AELrepeated. For children <12 years old, the exposure after dermal application exceeds the AELrepeated i.e the exposure is 156% of the AELrepeated when applied twice per day. It is therefore considered necessary to apply recommendations on maximum skin area to be applied twice per day with product in children <12 years old.

Reverse dose calculations show that only 6.1, 7.8, 4.9 and 2.3% of the estimated external dose per application at the 75th percentile of use for males, females, children >12 years and children< 12 years respectively can be ingested before an AEL acute (oral) of 0.75 mg/kg bw/day is exceeded. If as a worst case it is assumed that adults ingest the whole amount applied to fingers (4% of treated body area) they can apply a 15% Aerosol product 1.5 and 1.9 times a

day for males and females respectively. In children > 12 years old this corresponds to 0.62 times per day (assuming as a worst case that they ingest the whole amount applied to hands, i.e 8% of the exposed body surface). Equally for children <12years old, this corresponds to 0.23 times per day (assuming a worst case where they ingest the whole amount on hands i.e 10% of the treated body surface). However, the oral dose is considered to be largely overestimated given the short half life after oral exposure in dogs and rats and the rapid achievement of Cmax. When considering the representative product (OFF! Aerosol, 15% DEET), the oral contribution is considered negligible since the product contains Bitrex, a strong deterrent for ingestion, the product already also have recommendations on not to be used in children <2 years old and not to be used on children's hands. However these calculations show the importance of keeping this restriction. Furthermore, the product already has recommendations that it should not be used in children < 2 years old. The hand to mouth behaviour is more frequent in small children and based on concerns that Bitrex may not be sufficiently effective in protecting small children from ingestion of product, an age limit of 2 years is proposed together with recommendations that the product should not be applied to the hands of children <12 years old.

The risk characterisation is based on a traditional method comparing the estimated exposure with an AEL based on the dermal 90 day study in rats. The rat was less sensitive to neurotoxicity than dogs in the assessed tests, however plasma data comparing rat and human internal doses after dermal exposure indicate that there is a large margin between the species after dermal use. Furthermore, the NOAEL in rats were based on the highest dose tested. Based on this a standard factor of 100 was used in the assessment and considered enough, despite that dogs were more sensitive than rats. Furthermore, comparing plasma levels in dogs after oral exposure at a NOAEL level based on neurotoxicity yielded MOEs of 118, 261, 119 and 57 for adult males, adult females, children >12 years and children < 12 years respectively. This further supports the conclusions drawn from comparing the estimated exposure with an AEL using the dermal 90 day study in rats. Although it was concluded at TM II, 2009 that the plasma data were only to be included in the CAR as supportive to the conclusions drawn from the traditional method comparing the exposure with an AEL based on the dermal 90-day study in rats, these plasma data suggest that the MOE in children may actually be larger than 57.

There have been reports of adverse neurotoxic effects especially in children in the form of seizures after use of products containing DEET. However, considered the large number of estimated use, the risk seems to be very small. However it should be noted that idiopatic events of seizures in children makes it difficult to assess the causality of these effects. On the other hand, since the product is intended for intentional exposure on skin and to be used by the general public, including elderly, children and unhealthy subjects, a conservative approach should be taken when approving products. Special care should also be taken when approving products for use in children. When approving spray products, recommendations on ventilation should apply since the inhalational fraction is excluded in the risk characterisation calculations.

### *2.2.2. Environmental Risk Assessment*

#### 2.2.2.1. Fate and distribution in the environment

DEET is used in personal insect repellents (PT19) that are applied on uncovered human skin or clothing. The products containing DEET can be expected to be used both indoors and outdoors. However, the main route into the environment is assumed to be indirect and reach the water compartment, via STP effluents, derived from when the public bathe or shower after DEET application. According to level III fugacity modelling, the emissions will primarily affect the water compartment of aquatic environments.

Fate and effects data are only provided for the parent structure. DEET is considered to be ready biodegradable and no major (>10%) transformation products were formed in studies of hydrolysis and aquatic phototransformation.

DEET has a vapour pressure of 0.23 Pa (25°C) and a Henry's law constant of 3.93E-3 Pa*$m^3$/mol. The substance is predicted to have an atmospheric half-life of 0.63 days (15.2 hours). Thus an accumulation of DEET in air and long range transport is unlikely.

DEET is hydrolytically stable under acidic, basic and neutral conditions, and photolytically stable in sterile distilled water.

DEET is considered to be ready biodegradable and causes only minor inhibitory effects on (STP) microbial activity.

Because the substance will primarily end up in sewage treatment plants before any major release to the environment, final environmental exposure will to a large extent depend on whether households are connected to STPs equipped with at least secondary (biological) treatment.

DEET has a water solubility of 11.2 g/l (25°C) and its log Pow is 2.4 (22°C). Based on the calculated BCFs for aquatic and terrestrial organisms, DEET is considered to have very little or no potential to bioaccumulate.

DEET has a Koc of 43.3, suggesting that it is very mobile in soil and therefore could leach to the groundwater. However, DEET will not be directly emitted to soil and exposure via this route is therefore expected to be negligible.

#### 2.2.2.2. Effects assessment

Based on the results of acute toxicity studies, the EC/LC50 values for the tested organisms (*Oncorhynchus mykiss, Daphnia magna, and Selenastrum capricornutum*) are all in the same range (10-100 mg/l), although algae represented the most sensitive (ErC50 = 43 mg/l) of the three aquatic trophic levels tested. Thus the ErC50 for *Selenastrum capricornutum* serves as the key endpoint for the aquatic risk assessment. At a late stage during peer review it was concluded that the reported 96 h ErC50 is not strictly valid since the growth rate of the control slowed down during the 72-96 hours period. Since the 72 hour ErC50 (41 mg/l) was only marginally different from the 96 h value, as a pragmatic solution the PNECs were not amended.

The effect of DEET on aerobic biological sewage treatment processes was assessed by determining inhibition of respiration of the micro-organisms present in activated sludge following three hour contact. DEET had only a minor inhibitory effect on aquatic microbial activity (EC50 > 1000 mg/l).

Long term aquatic tests were not required since the acute tests did not indicate a danger, since the substance is ready biodegradable and primarily emitted to STP before reaching the aquatic

environment. There is also no significant difference between the acute EC50 values. No marine species were tested based on the presence of studies performed on freshwater species, all suggesting low toxicity, and DEET will not be used or released in marine environments in considerable amounts.

In the absence of any long-term toxicity endpoints and marine data, the TGD on Risk Assessment prescribes an assessment factor of 1000 for the freshwater environment and 10 000 for the marine environment.

For the sediment compartment, there is also no toxicity data available. The low Koc value indicates that sorption to sediment is low. Nevertheless, PNECsediment has been calculated based on equilibrium partitioning theory (Eq.P.) and PNECwater. The formulas used assume uptake from the water phase only. This assumption is accepted for DEET, because of its low log Pow and Koc values. No quantitative estimation of PNECmarine sediment is necessary because the PEC for the marine sediment compartment will be based on Eq.P. and the same log Pow and Koc values. The PEC/PNEC ratio for the marine sediment compartment will therefore be the same as for the corresponding water compartment.

No terrestrial toxicity tests were performed. DEET is not expected to reach the terrestrial environment in significant amounts, and because of a low log Pow, a low Koc and the substance being ready biodegradable, DEET is not likely to become accumulated in soil. Nevertheless, PNECsoil has been calculated based on equilibrium partitioning theory (Eq.P.) and PNECwater. The formulas used assume uptake from the water phase only. This assumption is accepted for DEET, because of its low log Pow and Koc values.

PNECs were not calculated for the air compartment. The physiochemical properties of DEET do not suggest that this substance will pose a risk to the atmospheric environment.

The low BCF values suggest that DEET has a low bioaccumulation potential. Therefore, no risk of secondary poisoning via ingestion of potentially contaminated food (e g earthworms or fish) by birds or mammals was identified. For the terrestrial compartment, the expected negligible exposure adds to this conclusion. No avian dietary tests were required. However, acute oral avian toxicity was investigated and LD50 was determined to 1375 mg/kg bw.

#### 2.2.2.3. PBT assessment

DEET does not meet any of the criteria for Persistent, Bioaccumulative and Toxic (PBT) substances or the very Persistent, very Bioaccumulative (vPvB) category.

#### 2.2.2.4. Exposure assessment and risk characterisation

The risks for the environment are characterized by comparing the toxicity of the substance (PNECs) with the exposure estimates (PECs).

PECs are derived from modelling and compared to measured data obtained from peer reviewed scientific literature. Based on some worst case assumptions, potential residues (PECs in any of the aquatic compartments are not expected to exceed 0.03 mg/l (water phase) or 5.7 µg/kg (sediment phase). The calculated PECs are either lower or in the same order of magnitude as the highest concentrations found in environmental monitoring data.

The conclusion of the quantitative risk assessment (PEC/PNEC ratios) is that no risks to non-target organisms from the use of DEET in insect repellents have been identified, even if

adopting a conservative (realistic worst case) scenario for the PEC calculations. None of the PEC/PNEC ratios exceed 1. The most crucial ratio is related to the marine environment (ratio 0.60), which is not surprising given the high assessment factor.

Because the substance is found to be ready biodegradable but has low abiotic degradation potential, final environmental exposure will to a large extent depend on whether households are connected to STPs equipped with at least secondary (biological) treatment.

No risk for bioaccumulation or secondary poisoning was identified. DEET is not expected to pose a risk to the atmospheric environment.

Conservative pore/groundwater PEC was above the drinking water limit of 0.1 µg/L and therefore PECgw was calculated using the FOCUS PEARL model. In all nine scenarios the calculated PECgw were below the drinking water limit.

Based on the above it can be concluded that DEET will not pose a significant risk to any of the environmental compartments.

There was however monitoring data reported from The Netherlands which may be considered as a cause for concern, since for a few of the samples (3 out of 189 samples) concentrations above the drinking water limit were reported. The accuracy of these results could however not be evaluated by the RMS.

#### *2.2.3. List of endpoints*

In order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

## 3. DECISION

### 3.1. Background to the Decision

The overall conclusion from the evaluation of N,N-diethyl-*meta*-toluamide (DEET) for use in product type 19 (repellents and attractants), for the category of user as humans, non-professional, is that it is possible for the MS to issue authorisations on products containing DEET in accordance with the conditions laid down in article 5 (1) (b), (c), (d) of directive 98/8/EC.

DEET is efficacious enough, based on the documentation received on the active substance DEET and the representative product, containing 15% DEET, for the proposed manner and areas of use of products intended as repellents without unacceptable risk neither to human health or the environment.

However, certain risk mitigation measures that reduce the exposure in children < 12 years old are necessary to remove those concerns for children that have been identified during the risk assessment for human health. These include but should not be limited to, no use in children < 2 years old, reducing the extent of use in children < 12 years by measures such as

recommendations on maximum area to be applied, recommendations on unsuitable exposure areas i.e. hands, and around eyes and mouth, and recommendations on maximum daily number of applications.

### 3.2. Decision regarding Inclusion in Annex I

The N,N-diethyl-*meta*-toluamide (DEET) shall be included in Annex I to Directive 98/8/EC as an active substance for use in product-type product type 19 (repellents and attractants), subject to the following specific provisions:

a) The active substance N,N-diethyl-*meta*-toluamide (DEET) shall have a minimum purity of 97%w/w

b) The product type is PT 19, Repellents and Attractants

c) The category of user is non-professional users

Other particular conditions: Member States shall ensure that authorisations are subject to the following conditions:

(1) Primary exposure of humans shall be minimized by considering and applying appropriate risk mitigation measures, including, where applicable, instructions for the amount and frequency of application of the product on human skin.

(2) Labels on products intended for application on human skin, hair or clothing shall indicate that the product is intended only for restricted use on children between two and twelve years old, and that it is not intended for use on children less than two years old, unless it can be demonstrated in the application for product authorisation that the product will meet the requirements of Article 5 and Annex VI without such measures.

(3) Products must contain deterrents for ingestion.

### 3.3 Elements to be taken into account by Member States when authorising products

It should also be noted that the current risk assessment does not include a risk assessment of simultaneous use with other products such as sun lotions, which could significantly affect the uptake of dermally applied repellents. Therefore this also has to be taken into consideration when authorising products. Inhalational exposure has not been taken into account in the current evaluation, therefore recommendations on ventilation or avoiding breathing in spray, is necessary on the product labels of spray formulations. Products should be labelled with the safety phrases S23: do not breathe gas/fumes/vapour/spray, S51: use only in well ventilated areas.

Products should only be used on small skin surfaces in children <12 years old. Therefore recommendations on maximum skin areas to be applied on children to reduce exposure in children < 12 years of age, should be included on product labels. Products should not contain higher concentration of active substance than needed, taking into account efficacy and

application frequency. The maximum number of daily applications should be taken into consideration and also product labelling addressing maximum daily number of applications.

In the specific case of areas of high risk to the general population from insect borne diseases, conditions of authorisation allowing reducing the restrictions may be considered only after a thorough consideration of the possible risks from using the product compared with the possible benefits in limiting the effects of the insect borne-disease.

MS should pay particular attention to skin irritative properties of products during product authorisation. The magnitude of the irritative properties should be assessed together with its acceptability for the purpose of use (i.e. as a leave on product for skin application) and the category of user (general use including for example children, elderly and users with conditions affecting the skin).

Moreover, monitoring methods for analysing residues of DEET in the air compartment might be required for authorisation of DEET containing biocidal products, whose use pattern result in significant exposure to the air compartment.

Member States may need to consider inclusion of DEET in national programs for monitoring groundwater.

Any potential for direct exposure to surface water as a consequence of swimming etc. has not been assessed at the European level.

Specified efficacy claims should be accompanied by relevant efficacy tests in relevant species. No efficacy tests were carried out on treated articles or clothing, therefore if such claims occur during product authorisation, they should be addressed with relevant tests. Furthermore, there is a difference between insect species: the time that the insect is repelled after application of the product (time to first bite) can differ between less then one hour to 6 hours and this has impact on number of applications and should therefore be addressed during product authorisation.

### 3.4. Requirement for further information

It is considered that the evaluation has shown that sufficient data have been provided to verify the outcome and conclusions, and permit the proposal for the inclusion of N,N-diethyl-meta-toluamide (DEET) in Annex I to Directive 98/8/EC.

However, further validation data to prove the applicability of the proposed analytical method for the water compartment is considered needed (The applicant has stated that further validation work is underway and the data will be submitted as soon as possible).

### 3.5. Updating this Assessment Report

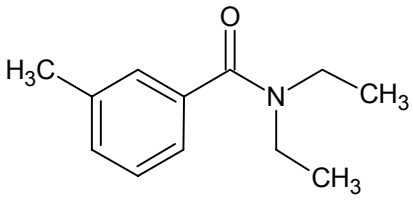
This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information referred to in Articles 7, 10.4 and 14 of Directive 98/8/EC. Such adaptations will be examined and finalised in connection with any amendment of the conditions for the inclusion of N,N-diethyl-meta-toluamide (DEET) in Annex I to the Directive.

# Appendix I: List of endpoints

## Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

| | |
|---|---|
| Active substance (ISO Common Name) | No ISO common name assigned.<br>Synonyms: N,N-diethyl-m-toluamide, DEET |
| Product-type | Insect repellent (PT 19) |

**Identity**

| | |
|---|---|
| Chemical name (IUPAC) | N,N-diethyl-m-toluamide |
| Chemical name (CA) | N,N-diethyl-3-methylbenzamide |
| CAS No | 134-62-3 |
| EC No | 205-149-7 |
| Other substance No. | Not assigned |
| Minimum purity of the active substance as manufactured (g/kg or g/l) | 970 g/kg |
| Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg) | DEET as manufactured does not contain any relevant impurities |
| Molecular formula | $C_{12}H_{17}NO$ |
| Molecular mass | 191.27 |
| Structural formula |  |

**Physical and chemical properties**

| | |
|---|---|
| Melting point (state purity) | <-20°C |
| Boiling point (state purity) | 284.2 °C (99.2% pure) |
| Temperature of decomposition | Not relevant as the boiling point was determined |
| Appearance (state purity) | Clear almost colourless liquid with a mild characteristic DEET odour (97.8% pure) |
| Relative density (state purity) | 0.998 (99.3% pure) |
| Surface tension | 58.0 mN/m at 20°C (98.6% pure) |
| Vapour pressure (in Pa, state temperature) | Extrapolated (99.4% pure):<br>0.11 Pa at 20°C<br>0.23 Pa at 25°C |
| Henry's law constant (Pa $m^3$ $mol^{-1}$) | 3.93 x $10^{-3}$ |
| Solubility in water (g/l or mg/l, state temperature) | 11.2 g/L at 25°C in distilled water with no pH |
| | No pH dependency expected as DEET cannot dissociate |
| Solubility in organic solvents (in g/l or mg/l, state temperature) | At 23°C (99.2% pure):<br>> 250 g/L in methanol, ethanol, hexane, acetonitrile, toluene and methylene chloride |
| | |
| Stability in organic solvents used in biocidal products including relevant breakdown products | Not relevant as DEET as manufactured does not contain any organic solvent. The stability of DEET in the solvent used in the representative product (i.e. ethanol) was confirmed by storage stability data. |
| | |
| Partition coefficient (log $P_{OW}$) (state temperature) | 2.4 at pH 6 and 22°C (99.2% pure) |
| | No pH dependency expected as DEET cannot dissociate |
| Hydrolytic stability ($DT_{50}$) (state pH and temperature) | See chapter 4 below. |
| Dissociation constant | Not determined. However based on the structure DEET is not able to dissociate at environmentally relevant pH. |
| UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength) | No absorbance maxima. ε ~0 at 290 nm in acidic, neutral and alkaline solutions. |
| Photostability ($DT_{50}$) (aqueous, sunlight, state pH) | See chapter 4 below. |
| Quantum yield of direct phototransformation in water at Σ > 290 nm | See chapter 4 below. |
| Flammability | Flash point: 144°C (98.6%) and it is therefore not a flammable liquid |
| Explosive properties | Not considered explosive based on theoretical considerations |

**Classification and proposed labelling**

| | |
|---|---|
| with regard to physical/chemical data | None |
| with regard to toxicological data | Class of danger: Xn, Xi<br>R phrases: 22, 36/38 |
| with regard to fate and behaviour data and ecotoxicological data | Class of danger: no<br>R phrases: 52 |

## Chapter 2: Methods of Analysis

**Analytical methods for the active substance**

| | |
|---|---|
| Technical active substance (principle of method) | GC-FID |
| Impurities in technical active substance (principle of method) | GC-FID with GC-MS for confirmation of identities |

**Analytical methods for residues**

| | |
|---|---|
| Soil (principle of method and LOQ) | DEET: LC-MS/MS with 1 transition (LOQ: 0.01 mg/kg) |
| Air (principle of method and LOQ) | No method considered required based on the use pattern and properties of DEET and the representative product.<br>A method might be required at the product-authorisation stage |
| Water (principle of method and LOQ) | A LC-MS/MS method taken from the open literature is proposed with a stated MRL (Method Reporting Limit) of 0.1 ng/L. However, further validation data is needed to verify the usefulness of the method for the natural water compartment. |
| Body fluids and tissues (principle of method and LOQ) | DEET in blood plasma:<br>HPLC-UV (LOQ 49.4µg/L)<br>No confirmatory method provided. No further data required as DEET is not classified as toxic or highly toxic |
| Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) | Not required as the use pattern of DEET will not results in any contact with food or feeding stuffs |
| Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) | Not required as the use pattern of DEET will not results in any contact with food or feeding stuffs |

# Chapter 3: Impact on Human Health

**Absorption, distribution, metabolism and excretion in mammals**

| | |
|---|---|
| Rate and extent of oral absorption: | oral abs: >80% based on urinary, faecal and tissue content (in the rat). In rats, 85-91% of administered radioactivity was found in urine |
| Rate and extent of dermal absorption: | Dermal rat approx. 82% (based on urinary excretion, faeces content, tissue content and skin ). Humans:<20% based on urinary excretion, faecal and skin content, corrected for recovery). No information was provided on inhalational absorption. |
| Distribution: | Highest concentrations in metabolising organs such as liver and kidney (dermal and oral dose). Following dermal administration residues in rat tissue were 0.15-0.67% |
| Potential for accumulation: | No accumulation determined in metabolism studies (rats, oral or dermal administration). |
| Rate and extent of excretion: | Rats: 74-91% in urine, 3-7% in feces (oral or dermal dose) and approximately 6.5% was recovered in skin samples, skin and enclosure rinses |
| Toxicologically significant metabolite(s) | None |

**Acute toxicity**

| | |
|---|---|
| Rat $LD_{50}$ oral | LD50 (males + females) =1892 mg/kg bw (95% Confidence Limits: 1652-2204 mg/kg bw) |
| Rat $LD_{50}$ dermal | LD50 (males & females) > 5000 mg/kg bw |
| Rat $LC_{50}$ inhalation | LD50 (males & females) > 2.02 mg/L (highest dose tested) |
| Skin irritation | Slightly irritating to skin |
| Eye irritation | Irritating to eyes |
| Skin sensitization (test method used and result) | Not a sensitizer (Buehler Method; U.S. EPA OPPTS Guideline 870.2600) |

**Repeated dose toxicity**

| | |
|---|---|
| Species/ target / critical effect | Dog (orally): clinical signs of neurotoxicity, body weight reduction (8 week study terminated after 5 days)<br>Rat (orally): body weight reductions<br>Rat, pig (dermally): dermal irritation at all doses tested (≥ 100 mg/kg bw/day) |

| | |
|---|---|
| Lowest relevant oral NOAEL / LOAEL | NOAEL (dog): 75 mg/kg bw/day (8 weeks 1 dose/day)<br>NOAEL (rat): 100 mg/kg bw/day (90 days, 2 year) |
| Lowest relevant dermal NOAEL / LOAEL | NOAEL (rat, pig) ≥1000 mg/kg bw/day |
| Lowest relevant inhalation NOAEL / LOAEL | Not applicable, no study performed |

| | |
|---|---|
| **Genotoxicity** | *In vitro* gene mutation in bacteria: Negative<br>*In vitro* cytogenicity in mammalian cells: Negative<br>*In vitro* gene mutation in mammalian cells: Negative in two separate studies |

**Carcinogenicity**

| | |
|---|---|
| Species/type of tumour | 2 year rat, 18 mo mouse: no treatment related tumors observed at highest dose tested |
| lowest dose with tumours | > 400 mg/kg bw/day (rat)<br>>1000 mg/kg bw/day (mouse) |

**Reproductive toxicity**

| | |
|---|---|
| Species/ Reproduction target / critical effect | Rat/ no reproduction target/ no critical effects, F1/F2 offspring, body weight reductions (paternal and maternal) |
| Lowest relevant reproductive NOAEL / LOAEL | NOAEL(reproduction/fertility)≥713 mg/kg bw/day<br>LOAEL (reproduction/fertility) >713 mg/kg bw/day<br>NOAEL (parental) 110 mg/kg bw/day<br>LOAEL (parental) 279 mg/kg bw/day<br>NOAEL (offspring) = 286 mg/kg bw/day<br>LOAEL (offspring) = 639 mg/kg bw/day |

Developmental toxicity

| | |
|---|---|
| Species/Developmental target / critical effect | (1) Rat/ no developmental target/ critical effects were signs of maternal toxicity (including mortality) and decreased fetal body weights<br>(2) Rabbit/ no developmental target/ critical effect was decreased maternal body weight gain |
| Lowest relevant developmental NOAEL / LOAEL | Maternal (rat):<br>NOAEL = 250.0 mg/kg/day<br>LOAEL = 750.0 mg/kg/day<br>Developmental (rat):<br>NOAEL = 250.0 mg/kg/day<br>LOAEL = 750.0 mg/kg/day<br>Maternal (rabbit):<br>NOAEL = 100.0 mg/kg/day<br>LO(A)EL = 325.0 mg/kg/day<br>Developmental (rabbit):<br>NOAEL = ≥ 325.0 mg/kg/day<br>LOAEL = > 325.0 mg/kg/day |

**Neurotoxicity / Delayed neurotoxicity**

| | |
|---|---|
| Species/ target/critical effect | Rat/ no target/ critical effects include (1) acute study - increased response time to heat stimulus and decreased rearing activity at one hour; and (2) chronic study - transient increase in locomotor activity |
| (1) Lowest relevant acute neurotoxicity NOAEL/LOAEL<br>(2)Lowest relevant developmental neurotoxicity NOAEL/LOAEL | (1) NOAEL = 200 mg/kg LOAEL = 500 mg/kg<br><br>(2) NOAEL Neurotox = 278 mg/kg bw/day<br>NOAEL Neuropath ≥ 683 mg/kg bw/day<br>LOAEL Neurotox = 683 mg/kg bw/day<br>LOAEL Neuropath > 683 mg/kg bw/day |

**Other toxicological studies**

| | |
|---|---|
| Mechanistic studies examining alpha$_{2u}$-globulin induced nephrotoxicity. Subchronic oral toxicity test in multiple strains of male rodents (rat) | Male rats: Charles River CD®, Fischer 344, NBRDietary/90 Day/0 and 400 mg/kg/day<br>Alpha$_{2u}$-globulin mediated kidney lesions observed at necropsy in CD and Fischer rats. No findings attributed to DEET exposure were observed in the NBR rat. |
| Mechanistic studies examining alpha$_{2u}$-globulin induced nephrotoxicity. Subchronic dermal toxicity test in castrated male rodents (rat) | Male rats: Castrated and Non-castrated; Charles River CD®<br>Dermal/90 Day (5 days/week)/0 and 1000 mg/kg/day<br>Alpha$_{2u}$-globulin mediated kidney lesions observed at a frequency of: treated non-castrated rats > treated castrated rats > untreated castrated rats. |

**Medical data**

| | |
|---|---|
| Medical surveillance data on manufacturing plant personnel, if available | Not applicable; DEET European Union Joint Venture members do not manufacture the a.s. in the EU. |
| Direct observation, *e.g.* clinical cases, poisoning incidents if available | The National Registry of Human Exposures to DEET collected detailed information from individuals who used DEET-containing insect repellents and reported serious adverse neurologic or systemic effects. Of 242 total cases, 12 cases of major (temporary) severity were *possibly* related to DEET (seizure, other neurological, dermal, and other) and one case of major severity was probably related to DEET (non-neurological). Fifty-nine cases with seizures were reported with 90% of the seizure cases of major or moderate severity. It was concluded that over 5 billion applications of DEET occurred in the population during the 7 year span of the Registry, and the overall risk of clinically significant adverse events is low.<br><br>Prognosis following poisoning: Information from the published literature ranges from full recovery to death (see 6.12.2) depending on the route of exposure and the magnitude of the overdose |

| | |
|---|---|
| | Sensitisation/allergenicity observations, if available: No medical data are available according to the applicant, indicating sensitization. Also, the a.s. has been shown to not be sensitising to humans in a clinical study (Annex Point B6.3(2), Document III-B). |
| Health records, both from industry and any other available sources | Not applicable; DEET European Union Joint Venture members do not manufacture the a.s. in the EU. |
| Epidemiological studies on the general population, if available | No epidemiological studies have been performed to the knowledge of the registrant. |
| Specific treatment in case of an accident or poisoning: first aid measures, antidotes and medical treatment, if known: First Aid Procedures: | Eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.<br><br>Skin: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.<br><br>Inhalation: Move person to fresh air. If person is not breathing, call an ambulance, then give artificial respiration, preferably by mouth-to-mouth if possible. Call a poison control center or doctor for further treatment advice.<br><br>Ingestion: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by a poison control center or doctor. Do not give anything by mouth to an unconscious person." |

| **Summary** | Value | Study | Safety factor |
|---|---|---|---|
| **Non-professional user** | | | |
| ADI (acceptable daily intake, external long-term reference dose) | Not applicable | Not applicable | Not applicable |
| AOEL-S (Operator Exposure) | Not applicable | Not applicable | Not applicable |
| $AEL_{acute}$ (general public) | 0.75 mg/kg bw/day | 8-week study (dogs, oral capsule) | 100 |
| $AEL_{repeated}$ (general public) | 8.2 mg/kg bw/day* | 90 day study (rat dermal) | 100 |
| ARfD (acute reference dose) | Not applicable | Not applicable | Not applicable |
| Professional user | Not applicable | Not applicable | Not applicable |

| | | | |
|---|---|---|---|
| Reference value for inhalation (proposed OEL) | Not applicable | Not applicable | Not applicable |

***Corrected for a dermal absorption of approximately 82 % in the rat**

| **Acceptable exposure scenarios (including method of calculation)** | |
|---|---|
| Professional users | Not relevant |
| Production of active substance: | Not relevant |
| Formulation of biocidal product | 15% DEET formulated as OFF!™ Aerosol spray |
| Intended uses | Non-professional use, direct application on skin |
| Secondary exposure | Neglible |
| Non-professional users | The exposure at the 75$^{th}$ percentile of use was 60,47, 74 and 156% of exposure for adult males, adult females, children >12 years and children < 12 years respectively. |
| Indirect exposure as a result of use | Not relevant |

## Chapter 4: Fate and Behaviour in the Environment

**Route and rate of degradation in water**

| | |
|---|---|
| Hydrolysis of active substance and relevant metabolites ($DT_{50}$) (state pH and temperature) | pH 4, 7, 9: $DT_{50} \geq 1$ year |
| Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites | DEET is photolytically stable in sterile distilled water and no degradation products were detected. |
| Readily biodegradable (yes/no) | Yes |
| Biodegradation in seawater | Not applicable |
| Non-extractable residues | Not applicable |
| Distribution in water / sediment systems (active substance) | Not applicable |
| Distribution in water / sediment systems (metabolites) | Not applicable |

**Route and rate of degradation in soil**

| | |
|---|---|
| Mineralization (aerobic) | Not determined |
| Laboratory studies (range or median, with number of measurements, with regression coefficient) | Not applicable |
| Field studies (state location, range or median with number of measurements) | Not applicable |
| Anaerobic degradation | Not determined |
| Soil photolysis | Not determined |
| Non-extractable residues | Not applicable |
| Relevant metabolites - name and/or code, % of | Not applicable |

| | |
|---|---|
| applied a.i. (range and maximum) | |
| Soil accumulation and plateau concentration | Not applicable |

**Adsorption/desorption**

| | |
|---|---|
| Ka , Kd | Not calculated |
| $Ka_{oc}$ , $Kd_{oc}$ | 43.3 |
| pH dependence (yes / no) (if yes type of dependence) | No |

**Fate and behaviour in air**

| | |
|---|---|
| Direct photolysis in air | DEET has a hydroxyl radical rate constant of 25.3E-12 $cm^3$/molecule·sec and an atmospheric half life of 15.2 hours (0.63 days), assuming a concentration of hydroxyl radicals of 0.5E06 mol/$cm^3$ (24-hour day period). |
| Quantum yield of direct photolysis | Not applicable |
| Photo-oxidative degradation in air | Not applicable |
| Volatilization | While the vapour pressure of the test substance exceeds the TGD criteria for volatile substances (> 0.01 Pa), the fraction of emissions to air as estimated by Level III fugacity modeling (EPI Suite v.3.11) is 2.74E-04% (according to the applicant, assuming a hydroxyl radical concentration of 1.5E06 mol/$cm^3$) or 4.02E-05% (according to the RMS, assuming a hydroxyl radical concentration of 0.5E06 mol/$cm^3$). |

**Monitoring data, if available**

| | |
|---|---|
| Soil (indicate location and type of study) | No data submitted by the applicant |
| Surface water (indicate location and type of study) | Supplemental literature data submitted by the applicant upon request by the RMS (see doc IIB) |
| Ground water (indicate location and type of study) | No data submitted by the applicant |
| Air (indicate location and type of study) | No data submitted by the applicant |

## Chapter 5: Effects on Non-target Species

**Toxicity data for aquatic species (most sensitive species of each group)**

| Species | Time-scale | Endpoint | Toxicity |
|---|---|---|---|
| **Fish** | | | |
| Fish (*Brachydanio rerio*) | 96 hours | $LC_{50}$ | 97 mg/L |

| | | | |
|---|---|---|---|
| **Invertebrates** | | | |
| Invertebrate (*Daphnia magna*) | 51 hours | $LC_{50}$ | 75 mg/L |
| **Algae** | | | |
| Algae (*Selenastrum capricornutum*) | 96 hours<br>72 hours | $E_rC_{50}$<br>$E_rC_{50}$ | 43 mg/L<br>41 mg/L |
| **Microorganisms** | | | |
| Not determined. | 3 hours | $EC_{50}$ | >1000 mg/L |

**Effects on earthworms or other soil non-target organisms**

| | |
|---|---|
| Acute toxicity | Not determined |
| Reproductive toxicity | Not determined |

**Effects on soil micro-organisms**

| | |
|---|---|
| Nitrogen mineralization | Not determined |
| Carbon mineralization | Not determined |

**Effects on terrestrial vertebrates**

| | |
|---|---|
| Acute toxicity to mammals | Not determined |
| Acute toxicity to birds | $LD_{50}$ = 1365 mg/kg bw |
| Dietary toxicity to birds | Not determined |
| Reproductive toxicity to birds | Not determined |

**Effects on honeybees**

| | |
|---|---|
| Acute oral toxicity | Not determined |
| Acute contact toxicity | Not determined |

**Effects on other beneficial arthropods**

| | |
|---|---|
| Acute oral toxicity | Not determined |
| Acute contact toxicity | Not determined |
| Acute toxicity to …….. | Not determined |

**Bioconcentration**

| | |
|---|---|
| Bioconcentration factor (BCF) | Aquatic: 22 (estimated)<br>Terrestrial (earthworms): 63.1 (estimated) |
| Depration time ($DT_{50}$)<br>($DT_{90}$) | Not determined |
| Level of metabolites (%) in organisms accounting for > 10 % of residues | Not determined |

## Chapter 6: Other End Points

None

# Appendix II: List of Intended Uses

## Summary of intended uses[4]

| Object and/or situation | Member State or Country | Product name | Organisms controlled[5] | Formulation | | Application | | | Applied amount per treatment | | | Remarks: |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Type | Conc. of a.s. | Method kind | Number min - max | interval between applications (min) | g a.s./L min - max | water L/m$^2$ min - max | g a.s./m$^2$ min - max | |
| Biting and sucking insects | EU | OFF!$^{TM}$ Aerosol | biting flies, biting midges or black flies (Ceratopogonidae, Simuliidae), chiggers, deer flies, no-see-ums, gnats, horse flies (Tabanidae), mosquitoes (Culicidae), fleas, | Aerosol | 15% (150 mg/kg) | Aerosol spray, direct dermal application | 1 - 2 times a day | To maintain efficacy | Not applicable | Not applicable | Not applicable | None |

4 adapted from: EU (1998a): European Commission: Guidelines and criteria for the preparation of complete dossiers and of summary dossiers for the inclusion of active substances in Annex I of Directive 91/414/EC (Article 5.3 and 8,2). Document 1663/VI/94 Rev 8, 22 April 1998

5 The summary of intended use are based on the notifier's proposal and is not exhaustive, sufficient tests were provided to show efficacy of the a.s as an repellent for an annex I uptake as PT 19, but more specified testing on specific organisms may be needed and should be addressed at MS level during product authorisation.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | sand flies (Phlebotomidae), stable flies, ticks, and small flying insects | | | | | | | | | |

# Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. These claims are based on information from the applicant. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

| Section No. | Author | Year | Title.<br>Socurce (where different from company), Company, Report No.<br>GLP (where relevant)/ (Un)Published | Data Protection Claimed (Yes/No)[1] | Owner[2] | Ref. No. |
|---|---|---|---|---|---|---|
| *Non Key Studies and Additional Supporting Literature References are Noted in Italics* | | | | | | |
| A3.5 | Sinning, DJ | 2004 | Physical and Chemical Characteristics of Diethyltoluamide: Boiling Point, Octanol/Water Partition Coefficient and Water Solubility. Case Consulting Laboratories, Inc., Study No. 1950-07 (unpublished) | Yes<br>Exist./First | EUJV | 101656 |
| *A3.6* | *Albert and Serjeant* | *1962* | *Ionization Constants of Acids and Bases, p138, Methuen & Co. Ltd. (published)* | *No* | *NA* | *n.a* |
| A3.7(1) | Sinning, DJ | 2001 | Physical and Chemical Characteristics of N,N-Diethyl-*m*-toluamide: UV/Visible Absorption and Solubility. Case Consulting Laboratories, Inc., Study No. 1550-13 (unpublished) | Yes<br>Exist./First | EUJV | 100077 |
| A3.7(2) | Lennan, TA | 1999 | Product Chemistry of DEET Technical. McLaughlin Gormley King Company, Project No. 1257 (unpublished) | Yes<br>Exist./First | EUJV | 100083 |
| A3.9 | Sinning, DJ | 2004 | Physical and Chemical Characteristics of Diethyltoluamide: Boiling Point, Octanol/Water Partition Coefficient and Water Solubility. Case Consulting Laboratories, Inc., Study No. 1950-07 (unpublished) | Yes<br>Exist./First | EUJV | 101656 |
| A3.11 | Lennan, TA | 1999 | Product Chemistry of DEET Technical. McLaughlin Gormley King Company, Project No. 1257 (unpublished) | Yes<br>Exist./First | EUJV | 100083 |
| A3.12 | Sydney, P | 2005 | DEET: Physicochemical Properties. Huntingdon Life Sciences Ltd., Study No. DCP003/052861 (unpublished) | Yes<br>Exist./First | EUJV | 101044 |
| A3.13 | Sydney, P | 2005 | DEET: Physicochemical Properties. Huntingdon Life Sciences Ltd., Study No. DCP003/052861 (unpublished) | Yes<br>Exist./First | EUJV | 101044 |
| A3.14(1) | Flack, I | 1999 | DEET: Relative Density and Viscosity Determinations. Huntingdon Life Sciences Ltd., Report No. CRI 019/994831 (unpublished) | Yes<br>Exist./First | EUJV | 100080 |
| A3.14(2) | Lennan, TA | 1999 | Product Chemistry of DEET Technical. McLaughlin Gormley King Company, Project No. 1257 (unpublished) | Yes<br>Exist./First | EUJV | 100083 |

| Section No. | Author | Year | Title.<br>Socurce (where different from company), Company, Report No.<br>GLP (where relevant)/ (Un)Published | Data Protection Claimed (Yes/No)[1] | Owner[2] | Ref. No. |
|---|---|---|---|---|---|---|
| *Non Key Studies and Additional Supporting Literature References are Noted in Italics* | | | | | | |
| *A3.15* | *United Nations* | *Draft* | *Consolidated Text of Draft Amendment to the Manual of Tests and Criteria supplement to the Model Regulations annexed to the tenth revised edition of the United Nations Recommendations on the transport of dangerous goods (ST/SG/AC.10/11rev.2).* | *No* | *NA* | *n.a.* |
| *A3.16* | *UK Health and Safety Executive* | *2001* | *Notification of new Substances Regulation UK, 1993: Oxidising Properties Guide, published by the UK Health and Safety Executive, 20 June 2001.* | *No* | *NA* | *n.a.* |
| A3.17 | Bergman, JT | 1999 | Storage Stability Evaluation & Corrosion Characteristic Evaluation of DEET Tech. McLaughlin Gormley King Company, Project No. GLP-1280 (unpublished) | Yes<br>Exist./First | EUJV | 101549 |
| A4.1(1) | Barwich, LS | 1998 | Standard Test Procedure: Analysis of N,N-Diethyl-meta-Toluamide (DEET) by Capillary GC Using Split Injection. Morflex, Inc., Morflex STP No. 93 M.24 (unpublished) | Yes<br>Exist./First | EUJV | 101664 |
| A4.1(2) | Bergman, JT | 2003 | Characterization by CAP-GLC for Impurities in in (SACIC) MGK Technical Diethyltoluamide. McLaughlin Gormley King Company, Project No. GLP-1693 (unpublished) | Yes<br>Exist./First | MGK | 101550<br>Confidential |
| | Bergman, JT | 2004 | Characterization by CAP-GLC for Impurities in in MGK Technical Diethyltoluamide (DEET). McLaughlin Gormley King Company, Project No. GLP-1859 (unpublished) | Yes<br>Exist./First | MGK | 101551<br>Confidential |
| A4.1(3) | Meinen, VJ | 1997 | CAP-GLC for Impurities in Nippon Technical Diethyltoluamide. McLaughlin Gormley King Company, Study No. GLP-1120 (unpublished) | Yes<br>Exist./First | MGK | 101548<br>Confidential |
| A4.1(4) | Sydney, P. | 2007 | Method Validation for Determination of the Active Substance and Impurities. Huntingdon Life Sciences, Ltd. Report No. MOX0012/073807. (unpublished) | Yes<br>Exist./First | VPM | 102311<br>Confidential |
| A4.2(a) | Sadgrove, L | 2005 | DEET: Validation of Methodology for the Determination of Residues in Soil. Huntingdon Life Sciences Ltd. Study No. DCP004/052633 (unpublished) | Yes<br>Exist./First | EUJV | 101043 |
| A4.2(c)(1) | Palmer, SJ, Kendall, TZ and Krueger, HO | 2002 | DEET: A 96-Hour Static Acute Toxicity Test with the Rainbow Trout (*Oncorhynchus mykiss)*. Wildlife International, Ltd., Project No. 538A-101 (unpublished) | Yes<br>Exist./First | EUJV | 100049 |
| A4.2(c)(2) | Kendall, T | 2002 | Analytical Method Verification for the Determination of DEET in Algal Medium. Wildlife International, Ltd., Project No.538C-101 (unpublished) | Yes<br>Exist./First | EUJV | 100050 |

| Section No. | Author | Year | Title.<br>Socurce (where different from company), Company, Report No.<br>GLP (where relevant)/ (Un)Published | Data Protection Claimed (Yes/No)[1] | Owner[2] | Ref. No. |
|---|---|---|---|---|---|---|
| *Non Key Studies and Additional Supporting Literature References are Noted in Italics* | | | | | | |
| A4.2(c)(3) | Vanderford, *et al.* | 2003 | Analysis of endocrine disruptors, pharmaceuticals, and personal care products in water using liquid chromatography/tandem mass spectrometry. *Anaytical Chemistry*. 75:6265-6274. | No | N/A | 008065 |
| A4.2(c)(3) | Trenholm *et al.* | 2006 | Broad range analysis of endocrine disruptors and pharmaceuticals using gas chromatography and liquid chromatography tandem mass spectrometry. *Chemosphere*. 65:1990-1998. | No | N/A | 008567 |
| A4.2(c)(3) | Trenholm *et al.* | 2008 | Determination of household chemicals using gas chromatography and liquid chromatography with tandem mass spectrometry. J*ournal of Chromatography A*. 1190:253-262. | No | N/A | 008547 |
| A4.2(c)(3) | Vanderford and Snyder | 2006 | Analysis of Pharmaceuticals in Water by Isotope Dilution Liquid Chromatography/Tandem Mass Spectrometry. *Environ. Sci. Technol*. 40:7312-7320. | No | N/A | 009059 |
| A4.2(c)(3) | Benotti *et al.* | 2009 | Pharmaceuticals and Endocrine Disrupting Compounds in U.S. Drinking Water. *Environ. Sci. Technol*. 43(3)597-603. | No | N/A | 008937 |
| A4.2(c)(3) | S. Snyder | 2009 | Personal communications with (Southern Nevada Water Authority) via telephone (7 May 2009) and email (April 2009). | No | N/A | N/A |
| A4.2(d) | Ohayon, A, Ehler, L and Denver, K | 1997 | A Blood Level Study in Humans Following Topical Application of N,N-Diethyl-*m*-Toluamide (DEET). LAB Pharmacological Research International, Inc., Project No. EP135 (unpublished) | Yes<br>Exist./First | JV | 100041 |
| A6.1.1 | Moore, GE | 2000a | Acute Oral Toxicity with DEET Insect Repellent. Product Safety Labs, Project No. 8392 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100056 |
| A6.1.2(1) | Moore, GE | 2001a | Acute Dermal Toxicity Study – Limit Test with N,N-Diethyl-*m*-toluamide. Product Safety Labs, Project No. 10883 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100060 |
| A6.1.2(2) | Moore, GE | 1999 | MGK Technical DEET: Acute Dermal Toxicity Study in Rabbits – Limit Test. Product Safety Labs, Project No. 6836 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100061 |
| A6.1.3 | Moore, GE | 2000b | Acute Inhalation Toxicity Test with DEET Insect Repellent. Product Safety Labs, Project No. 8394 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100062 |
| A6.1.4(1) | Moore, GE | 2000c | Primary Skin Irritation Test with DEET Insect Repellent. Product Safety Labs, Project No. 8396 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100069 |

| Section No. | Author | Year | Title.<br>Socurce (where different from company), Company, Report No.<br>GLP (where relevant)/ (Un)Published | Data Protection Claimed (Yes/No)[1] | Owner[2] | Ref. No. |
|---|---|---|---|---|---|---|
| *Non Key Studies and Additional Supporting Literature References are Noted in Italics* | | | | | | |
| A6.1.4(2) | Moore, GE | 2001b | Primary Eye Irritation Study in Rabbits with N,N-Diethyl-*m*-toluamide. Product Safety Labs, Project No. 10885 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100066 |
| A6.1.5 | Moore, GE | 2001c | Dermal Sensitization Study in Guinea Pigs (Buehler Method) with N,N-Diethyl-*m*-toluamide. Product Safety Labs, Project No. 10887 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100073 |
| A6.2(1) | Selim, S | 1991 | Pharmacokinetics and Comparative Dermal Absorption Study of N,N-Diethyl-*m*-Toluamide (DEET) in the Rat. Biological Test Center, Study No. P01836 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100037 |
| A6.2(1) | Selim, S | 1991 | Addendum to the Report – Pharmacokinetics and Comparative Dermal Absorption Study of N,N-Diethyl-*m*-Toluamide (DEET) in the Rat. Biological Test Center, Study No. P01836 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100037_<br>Addendum |
| A6.2(2) | Lin, P and Selim, S | 1991 | Determination of Expired $^{14}C$ Volatiles Following a Single Oral or Dermal Dose of N,N-Diethyl-*m*-Toluamide (DEET) in the Rat. Biological Test Center, Study No. P01862 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100036 |
| A6.2(3) | Selim, S | 1992 | Absorption and Mass Balance of $^{14}C$-DEET After Topical Administration to Healthy Volunteers. Biological Test Center, Study No. P891002 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100039 |
| A6.2(4) | Ohayon, A, Ehler, L and Denver, K | 1997 | A Blood Level Study in Humans Following Topical Application of N,N-Diethyl-*m*-Toluamide (DEET). LAB Pharmacological Research International, Inc., Project No. EP135 (unpublished) GLP | Yes<br>Exist./First | JV | 100041 |
| A6.2(5) | Goldenthal, EI | 1999 | 48-Hour Blood Level Study in Rats Following a Single Oral Bolus Administration of N,N-Diethyl-*m*-Toluamide (DEET) in the Rat. MPI Research Inc., Project No. 555-032 (unpublished) GLP | Yes<br>Exist./First | JV | 100043 |
| A6.2(6) | Badalone, V | 1997 | Blood Level Study in Dogs Following Oral Administration, via Gelatin Capsules, of N,N-Diethyl-*m*-Toluamide (DEET). LAB Pharmacological Research International, Inc., Project No. 87607 (unpublished) GLP | Yes<br>Exist./First | JV | 100044 |
| A6.2(7) | Laveglia, J | 1998 | Blood Level Study in Rats Following Single and Repeated Dermal Applications of N,N-Diethyl-*m*-Toluamide (DEET). MPI Research Inc., Project No. 555-029 (unpublished) GLP | Yes<br>Exist./First | JV | 100046 |

| Section No. | Author | Year | Title.<br>Socurce (where different from company), Company, Report No.<br>GLP (where relevant)/ (Un)Published | Data Protection Claimed (Yes/No)[1] | Owner[2] | Ref. No. |
|---|---|---|---|---|---|---|
| *Non Key Studies and Additional Supporting Literature References are Noted in Italics* | | | | | | |
| A6.3.1(1) | Goldenthal, EI | 1995a | Evaluation of DEET in an Eight-Week Oral Gelatin Capsule Toxicity Study in Dogs. International Research and Development Corporation, Project No. 555-027 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100020 |
| A6.3.1(2) | Goldenthal, EI | 1997 | Evaluation of DEET in an Eight-Week Oral Toxicity Study in Dogs. MPI Research and Development Corporation, Project No. 555-026 (unpublished) GLP | Yes<br>Exist./First | JV | 100019 |
| A6.4.1 - *Additional Non Key Studies Submitted for this Endpoint*<br>*(Doc. II- 3.5)* | *Johnson, DE* | *1987c* | *Evaluation of DEET in a 90-Day Oral Dose Range Finding Study in Mice. International Research and Development Corporation, Project No. 555-002 (unpublished) GLP* | *Yes*<br>*Exist./Previous* | *JV* | *100023* |
| A6.4.1 - *Additional Non Key Studies Submitted for this Endpoint*<br>*(Doc. II-3.5)* | *Goldenthal, EI* | *1989* | *Evaluation of DEET in a 90-Day Dose Range Finding Study in Hamsters. International Research and Development Corporation, Project No. 555-012 (unpublished) GLP* | *Yes*<br>*Exist./Previous* | *JV* | *100007* |
| A6.4.1(1) | Johnson, DE | 1987a | Evaluation of DEET in a 90-Day Oral Dose Range Finding Study in Rats. International Research and Development Corporation, Project No. 555-001 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100026 |
| A6.4.2(2) | Johnson, DE | 1987b | Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Rats. International Research and Development Corporation, Project No. IRDC 555-003 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100013 |
| A6.5(1) | Goldenthal, EI | 1994 | Evaluation of DEET in an One-Year Chronic Oral Toxicity Study in Dogs. International Research and Development Corporation, Project No. 555-021 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100021 |
| A6.5(2) | Goldenthal, EI | 1995b | Evaluation of DEET in a Two-Year Dietary Toxicity and Oncogenicity Study in Rats. International Research and Development Corporation, Project No. 555-023 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100027 |
| A6.6.1 | San, RHC and Schadly, MB | 1989 | Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay. Microbial Associates, Inc., Study No. T8728.501014 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100033 |

| Section No. | Author | Year | Title.<br>Socurce (where different from company), Company, Report No.<br>GLP (where relevant)/ (Un)Published | Data Protection Claimed (Yes/No)[1] | Owner[2] | Ref. No. |
|---|---|---|---|---|---|---|
| *Non Key Studies and Additional Supporting Literature References are Noted in Italics* | | | | | | |
| A6.6.2 | Putman, DL and Morris, MJ | 1989 | Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. Microbial Associates, Inc., Study No. T8728.337 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100034 |
| A6.6.3(1) | Curren, RD | 1989 | Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with a Confirmatory Assay. Microbial Associates, Inc., Study No. T8728.380009 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100035 |
| A6.6.3(2) | Paika, IJ | 1993 | CHO/HGPRT Forward Mutation Assay. Toxikon Corporation, Study No. 93G-1041 (unpublished) | Yes<br>Exist./First | EUJV | 100074 |
| A6.7(1) | Goldenthal, EI | 1995b | Evaluation of DEET in a Two-Year Dietary Toxicity and Oncogenicity Study in Rats. International Research and Development Corporation, Project No. 555-023 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100027 |
| A6.7(2) | Goldenthal, EI | 1990 | Evaluation of DEET in an Eighteen Month Dietary Oncogenicity Study in Mice. International Research and Development Corporation, Project No. 555-005 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100024 |
| A6.8.1(1) | Neeper-Bradley, TL | 1990 | Developmental Toxicity Evaluation of DEET Administered by Gavage to CD® (Sprague-Dawley) Rats. Bushy Run Research Center, Project No. 52-603 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100030 |
| A6.8.1(2) | Chun, JS and Neeper-Bradley, TL | 1991 | Developmental Toxicity Evaluation of DEET Administered by Gavage to New Zealand White Rabbits. Bushy Run Research Center, Project No. 54-597 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100032 |
| A6.8.2 | Schardein, JL | 1989 | Evaluation of DEET in a Two Generation Reproduction/Fertility Study in Rats. International Research and Development Corporation, Project No. 555-004 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100028 |
| A6.9(1) | Schardein, JL | 1990a | Neurotoxicity Evaluation in Rats Following Acute Oral Exposure to DEET. International Research and Development Corporation, Project No. 555-017 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100003 |
| A6.9(2) | Schardein, JL | 1990b | Neurotoxicity Evaluation in Rats Following Multigeneration Exposure to DEET. International Research and Development Corporation, Project No. 555-015 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100004 |
| A6.10(1) | Goldenthal, EI | 1992 | Evaluation of DEET in a Multistrain 90-Day Dietary Renal Toxicity Study in Rats. International Research and Development Corporation, Project No. 555-022 (unpublished) | Yes<br>Exist./Previous | JV | 100025 |

| Section No. | Author | Year | Title.<br>Socurce (where different from company), Company, Report No.<br>GLP (where relevant)/ (Un)Published | Data Protection Claimed (Yes/No)[1] | Owner[2] | Ref. No. |
|---|---|---|---|---|---|---|
| *Non Key Studies and Additional Supporting Literature References are Noted in Italics* | | | | | | |
| A6.10(2) | Goldenthal, EI | 1989 | Evaluation of DEET in a 90-Day Dermal Toxicity Study in Castrated Male Rats. International Research and Development Corporation, Project No. 555-010 (unpublished) GLP | Yes<br>Exist./Previous | JV | 100014 |
| A6.11 | Piccirilli, G | 1999 | A Study to Determine the Half-life and Volume of Distribution of N,N-Diethyl-*m*-Toluamide (DEET) When Administered by a Single Bolus Intravenous Injection in Two Beagle Dogs. ClinTrials BioResearch Laboratories Ltd., Project No. 45133 (unpublished) GLP | Yes<br>Exist./First | JV | 100047 |
| A6.12 | Schoenig, GP and Osimitz, TG | 2001 | DEET. In: Krieger, R., ed, *Handbook of Pesticide Toxicology*, Vol 2. Agents, San Diego: Academic Press, pp. 1439-1459. (published) | No | NA | 006993 |
| A6.12. | Osimitz, TG | 2006 | Safety Assessment of Insect Repellents Containing N,N-Diethyl-m-toluamide (DEET) – Information from the DEET Registry. Presented at the 2006 Conference on West Nile Virus and at the 2006 Meeting of the American Mosquito Control Association (published) | No | NA | 007792 |
| A7.1.1.1.1 | Lezotte, FJ and Nixon, WB | 2002 | DEET: An Evaluation of Hydrolysis as a Function of pH. Wildlife International, Ltd., Project No. 538C-103 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100055 |
| A7.1.1.1.2 | Swan, G | 2006 | DEET: Phototransformation in Water. Huntingdon Life Sciences Ltd. Study No., DCP0045/053423 (unpublished) GLP | Yes<br>Exist./First | EUJV | 101627 |
| A7.1.1.2.1 | Schaefer, EC and Siddiqui, AI | 2002a | Ready Biodegradability by the Carbon Dioxide Evolution Test Method. Wildlife International, Ltd., Project No. 538E-102 (unpublished) GLP | Yes<br>Exist./First | EUJV | 100052 |
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[1] Exist./Previous: Data on existing [a.s./b.p.] submitted under national legislation prior to submission for entry into Annex I/IA
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[2] JV = DEET Joint Venture
EUJV = DEET European Union Joint Venture
SCJ = S.C. Johnson EurAFNE Ltd.
NA = Not applicable; published

VPM=Vertellus Performance Materials Inc