Proposed Re-evaluation Decision PRVD2025-09

DEET plus related active toluamides and Its associated end-use products

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Proposed re-evaluation decision for DEET plus related active toluamides and associated end-use products

Under the authority of the *Pest Control Products Act,* all registered pesticides must be re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

DEET plus related active toluamides (hereafter referred to as DEET) is a personal insect repellent applied either to clothing or directly to skin, to protect people from biting and nuisance insects.

Currently registered products containing DEET can be found in the Pesticide Product Information Database and in Appendix I. Appendix II lists all uses for which DEET is presently registered. There are no Commercial Class products. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the re-evaluation of DEET.

This document presents the proposed re-evaluation decision for DEET, including the proposed amendments (risk mitigation measures) to protect human health and the environment, as well as the science evaluation on which the proposed decision is based. All products containing DEET that are registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period,[1] during which the public (including the pesticide manufacturers and stakeholders) may submit written comments and additional information to PMRA Publications. The final re-evaluation decision will be published after taking into consideration the comments received during the consultation period that are directly related to this proposed re-evaluation decision.

Proposed re-evaluation decision for DEET

Health Canada, under the authority of the *Pest Control Products Act,* has conducted evaluations considered necessary with respect to the health and environmental risks and value of DEET based on available scientific information in accordance with subsection 16(6) of the *Pest Control Products Act*. Based on these evaluations, Health Canada is proposing for public consultation, pursuant to section 28 of the *Pest Control Products Act*, the continued registration of DEET and associated end-use products registered for sale and use in Canada under section 21 of the *Pest Control Products Act*.

With respect to human health, potential risks were shown to be acceptable when DEET is used according to current conditions of registration. Label improvements are proposed to meet current labelling standards and clarify existing label statements.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

The risks to the environment were shown to be acceptable when DEET is used according to current conditions of registration.

DEET has value as an insect repellent used on human skin and clothing to protect people from biting and nuisance insects. DEET works by making it hard for the insects to detect users. DEET is used in 201 personal insect repellents currently registered, and is a valuable tool to protect people from biting insects that may also be vectors for insect-borne diseases.

Risk mitigation measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health, the environment and ensure the product has acceptable value which must be followed by law. The proposed label amendments as a result of the re-evaluation of DEET, are summarized below. Refer to Appendix VI for details.

Human health

Label improvements to meet current standards:

- Updated precaution and direction of use statements for both the technical grade and domestic-class end-use products.

International context

DEET is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the European Union, Australia, New Zealand and the United States. Internationally and within the available information, no evidence of a ban as of 24 March 2025 to prohibit all uses of DEET for health or environmental reasons has been identified. DEET is currently under registration review by the USEPA.

Next steps

Upon publication of this proposed re-evaluation decision, the public, including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period.

Health Canada will accept written comments on this proposal up to 90 days from the date of publication of this document ("consultation period"). Comments on the proposed decision can be submitted during the consultation period to the PMRA through PMRA Publications, or the Public Engagement Portal (Public Engagement Forms - Consultation Comment). For more information or if you have questions, contact the PMRA's Pest Management Information Service.

Before making a re-evaluation decision on DEET under section 21 of the *Pest Control Products Act*, the comments received during the consultation period that are directly related to this proposed decision, such as comments directed to the Science evaluation, will be taken into consideration in preparation of the final re-evaluation decision document. A science-based

approach will be applied in making a final decision on DEET. In accordance with subsection 28(5) of the *Pest Control Products Act*, Health Canada will then publish a final re-evaluation decision document, which will include the decision, the reasons for it, a summary of the comments received directly related to the proposed re-evaluation decision during the consultation period, and Health Canada's response to these comments.

Refer to Appendix I for details on specific products impacted by this proposed decision.

Other information

The relevant confidential test data on which the proposed decision is based (as documented in the References of this document) are available for public inspection, upon application, in PMRA's Reading Room. For more information, please contact the Pest Management Information Service.

Additional scientific information

Additional scientific data are not required at this time.

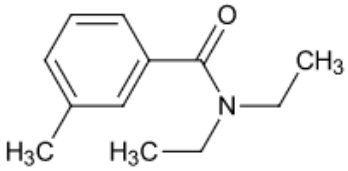
Science evaluation

1.0 Introduction

DEET is registered for use as a personal insect repellent (Use-Site Category 26: human skin, clothing and proximal sites) to repel mosquitoes, black flies, stable flies, ticks, chiggers, biting midges and deer flies. As of 23 July 2025, there are a total of 205 products containing DEET including two (2) technical grade active ingredients (Aurorium LLC and Clariant Corporation), one (1) manufacturing concentrate product (Aurorium LLC), and 202 domestic-class end-use products (30 registrants) containing DEET registered in Canada. Currently registered products containing DEET can be found in Appendix I. Appendix II lists all the uses for which DEET is presently registered.

2.0 Technical grade active ingredient

2.1 Identity

Common name	DEET (approved by ANSI and the Entomological Society of America)
Function	Insecticide
Chemical family	Toluamide
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	EN: *N,N*-diethyl-3-methylbenzamide FR: 3-méthyl-*N,N*-diéthylbenzamide
2 Chemical Abstracts Service (CAS)	*N,N*-diethyl-3-methylbenzamide
CAS registry number	134-62-3
Molecular formula	C12H17NO
Structural formula	
Molecular weight	191.27

Registration number	**Purity of the technical grade active ingredient**
18068	98.97% (+ 0.15% related active toluamides)
23785	98.5% (+ 0.38% related active toluamides)

2.2 Physical and chemical properties

Property	Result
Vapour pressure at 25°C	0.27 Pa
Ultraviolet (UV) / visible spectrum	No absorbance at $\lambda > 300$ nm
Solubility in water at 20°C	9.6 µg/mL at pH 7.4
n-Octanol/water partition coefficient	Log K_{ow} = 2.02
Dissociation constant	Based on its structure, no dissociation is expected at environmentally relevant pH

3.0 Human health assessment

3.1 Toxicology summary

DEET plus related active toluamides technical active ingredient is a mixture of DEET (N,N-diethyl-m-toluamide) and related active toluamides (ortho and para isomers), which is known to have repellent properties for blood-sucking arthropods. DEET plus related active toluamides, hereafter referred to as DEET, is registered for use as a personal insect repellent.

A detailed review of the toxicology database for DEET was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment. Several additional studies were submitted in the context of the re-evaluation, including a toxicokinetic study in dogs, acute in vivo toxicity studies in rats, rabbits, and guinea pigs, a short-term oral toxicity study in dogs, and an in vitro genotoxicity study. The majority of the available studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The human health hazard assessment also considered information retrieved from the published scientific literature. Overall, the scientific quality of the toxicology database is acceptable, and the database is considered adequate to characterize the potential health hazards associated with DEET.

Available toxicokinetic and metabolism data consisted of studies in which radiolabelled DEET was administered via oral gavage to rats, or via the dermal route to rats, mice, or humans. Toxicokinetic studies were also available in which non-radiolabelled DEET was administered to dogs via the oral (capsule) or intravenous routes, to humans via the dermal route, or to rats via the oral or dermal routes. In vitro metabolism studies using rat, mouse, and/or human liver microsomes, as well as human P450 isoforms were also available.

In rats (PMRA No. 1126612), DEET was rapidly and extensively absorbed and widely distributed into all tissues following oral dose administration. Absorption was significantly slower following dermal dosing. Blood radioactivity during the first 24 hours post-dose and tissue radioactivity at peak blood concentrations were more than an order of magnitude lower following dermal dosing compared to a similar oral dose. Following oral dosing, at the time of peak blood concentrations, the highest tissue concentration was detected in the kidneys. DEET was rapidly eliminated, primarily in the urine, regardless of dosing regimen. Elimination in the feces was low and no appreciable amount of DEET was excreted in expired air. There was no evidence of tissue retention in any of the available studies.

Whole body autoradiography of mice following a single dermal application showed highest concentrations of radioactivity in the lacrimal gland, liver, kidney, and nasal mucosa two hours post-dosing. There were also higher concentrations in the bile, intestinal contents, and urine, indicative of biliary and urinary excretion. Six days post-dosing, radioactivity was only detected on the skin at the application site and in the urinary bladder.

Several studies measuring DEET levels in plasma following DEET administration were performed in dogs (oral and intravenous exposure; PMRA No. 1176461, PMRA No. 2934207) and in rats (oral and dermal exposure; PMRA No. 1190674, PMRA No. 1176460) to compare plasma levels with those in humans (dermal exposure; PMRA No. 2246887, PMRA No. 1176163).

In dogs, after four repeated capsule-administered doses of non-radiolabelled compound, DEET was rapidly absorbed from the gastrointestinal tract with maximum plasma concentrations occurring within 10 to 60 minutes. The mean plasma elimination half-life was 28 minutes, indicating rapid elimination. A similar pharmacokinetic profile was observed following intravenous administration in dogs with peak plasma concentration reached five minutes post-dose and an elimination half-life of 45 minutes.

In rat studies, females consistently showed higher mean peak DEET plasma levels than males following both oral and dermal dosing. After oral administration, peak plasma levels occurred within 15 to 45 minutes. Elimination of DEET from plasma was biphasic. DEET was rapidly absorbed from the stomach followed by distribution in the body within 2 to 4 hours of administration, and then subsequently eliminated from plasma within 12 hours. Following a single dermal dose, mean peak plasma concentrations occurred at 4 and 8 hours in males and females respectively. Although some variability was observed across studies, peak plasma concentrations were consistently lower after dermal dosing compared to equivalent oral doses.

Plasma levels of DEET were also monitored in human volunteers following a single (PMRA No. 2246887) or repeated (PMRA No. 1176463) dermal application for four consecutive days. While the PMRA does not utilize systemic toxicity studies conducted in humans to support pesticide health assessments due to ethical and safety concerns, other types of studies involving human participants, such as pharmacokinetic, exposure, and insect repellent efficacy studies, may be considered.[2] In the current evaluation, pharmacokinetic data from human studies were

[2] SPN2016-01 - Restricted Use of Human Studies with Pesticides for Regulatory Purposes.

incorporated to inform the hazard assessment. Following a single dermal application, DEET plasma levels increased gradually, with time to peak plasma levels generally being reported at 8 to 9 hours. The mean peak plasma values on day 1 were slightly higher in male compared to female volunteers. A similar trend in plasma levels was noted after four consecutive days of applications. This sex difference was opposite to that observed in rat studies. Following both single and repeated exposure, the DEET plasma concentrations were below the limit of quantification within 24 hours of application. A comparison of peak plasma levels between rats and humans following equivalent dermal dosing showed that the levels in rats were at least one order of magnitude higher than in humans, suggesting higher absorption following dermal exposure in rats compared to humans.

In rats, DEET was fully metabolized and a similar metabolic profile was observed following both oral and dermal exposure. The majority of the excreted urinary radioactivity (approximately 50–60%) was associated with the metabolite 3-(diethylcarbamoyl)benzoic acid (DCBA), which resulted from oxidation of the methyl group to carboxylic acid. A second metabolite, m-((ethylamino)carbonyl) benzoic acid (EACB), formed through dealkylation of the amide group, accounted for 3 to 17% of the administered radioactivity. The urinary metabolic profile of DEET was also characterized in humans following a single dermal exposure (PMRA No. 2246887). Following dermal exposure, absorption in humans was lower than in rats; however, the metabolic profile was similar between the two species. In humans, absorbed DEET was fully metabolized prior to excretion in urine. Six urinary metabolites were identified, with DCBA accounting for 24 to 42% and EACB for 8 to 25% of the total urinary radioactivity.

The metabolism of DEET in various species was also assessed in in vitro metabolism studies. While there were limitations with these studies, the results suggested that DEET is primarily metabolized by liver oxidases in humans. Intrinsic clearance rates were reported to be similar between human and mouse liver microsomes, whereas significantly higher clearance was observed in rat microsomes, suggesting that DEET was more efficiently metabolized in this species. Metabolites identified for all three species in the in vitro studies included N-ethyl-m-toluamide (ET) and N,N-diethyl-m-(hydroxymethyl)benzamide (DHMB),[3] and it was reported that there was preferential formation of DHMB by all species tested.

DEET was of slight acute toxicity via the oral route and of low acute toxicity via the dermal and inhalation routes in rats. DEET was moderately irritating to rabbit eyes and minimally to mildly irritating to rabbit skin. DEET was not a potential dermal sensitizer in the guinea pig via the Buehler test.

In short-term oral toxicity studies conducted with DEET in hamsters, mice, rats, and dogs, decreased body weight, body weight gain and food consumption were the most commonly observed effects in all species. Additional findings in hamsters and rats in 90-day dietary studies at higher dose levels included findings in the male reproductive system in hamsters and altered kidney and liver weights in female rats. The mouse was the least sensitive species, with effects in the 90-day dietary study only occurring above the limit dose of testing (>1000 mg/kg bw/day).

[3] Referred to in the published study report as BALC (PMRA No. 3607612).

In male rats, kidney lesions, including chronic inflammation, hyaline droplet formation and granular cast accumulation in the renal tubules, as well as tubular epithelial regeneration were often noted following short-term oral and dermal dosing. This renal pathology was associated with an accumulation of alpha 2u-globulin in renal tubules. Mechanistic data were provided to support the involvement of alpha 2u-globulin accumulation in renal tubules as the underlying cause of the observed nephrotoxicity in male rats. Alpha 2u-globulin is synthesized in the liver of adult male rats, secreted into the general circulation, and reabsorbed by the renal proximal tubule cells. The critical role of this protein in the renal effects of DEET was demonstrated by the absence of histopathological changes in female rats, and in the NCI-Black-Reiter (NBR) rat strain that does not synthesize alpha 2u-globulin. Since humans do not produce alpha 2u-globulin, the observed kidney findings in male rats were not considered to be a relevant endpoint for human risk assessment purposes.[4]

In short-term toxicity studies in dogs, various dosing regimens were explored in range-finding studies since palatability issues led to adverse clinical signs of toxicity and limited the dose level at which DEET could be administered via the diet. Gelatin capsules were initially used to increase the dose level and avoid the palatability issues; however, single bolus administration via gelatin capsules resulted in severe clinical signs of toxicity (decreased activity, twitching, emesis, ptyalism, and abnormal head movements). Therefore, the daily dose was divided into two doses, with dogs receiving one dose in the morning and another afternoon dose via gelatin capsules. This dose-splitting exposure was used in the 12-month definitive study. The main findings observed in the definitive study included decreased body weight, clinical signs of toxicity such as decreased defecation and tremors, and brown pigment on the mandibular lymph nodes at the mid-dose level, and ptyalism, abnormal head movement, ataxia, and blood findings at the highest dose tested.

The effects of dermal exposure to DEET were explored in rats and micropigs. In a 90-day dermal toxicity study in rats, dermal irritation as well as histopathological changes in kidneys in males were observed at all doses tested. As noted above, the kidney findings in males were not considered relevant to the human risk assessment. At the highest dose tested in rats, which was also the limit dose of testing, body weight effects and kidney findings in females were noted. In a 90-day dermal toxicity study in the micropig, there were no adverse systemic effects up to the limit dose of testing. Dermal irritation was observed at all doses tested. A repeat-dose inhalation toxicity study was not available.

In long-term dietary toxicity studies in mice and rats, adverse effects were only observed at the highest doses tested, which in the mouse study was the limit dose. Decreased body weight was observed in both sexes in mice and in female rats. In mice, increased incidences of enlarged spleen and lymphoid hyperplasia of the spleen were also observed in both sexes, and inflammation of the salivary gland and urinary bladder were observed in males. Additionally, an equivocal increase in the incidence of hyperplastic nodules of the liver was observed in both sexes at the mid- and high-dose levels. In rats, a slight increase in mild hemorrhage of the pituitary gland was noted in both sexes. In males, testes weights were increased; however, there

[4] Report of the EPA Peer Review Workshop Report on Alpha2u-Globulin: Association with Renal Toxicity and Neoplasia in the Male Rat, 1991. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=3000484L.tx

were no corresponding histopathological changes. In females, an increase in liver weight and inflammation was also noted.

There were no treatment-related tumours observed in rat or mouse long-term dietary toxicity studies. DEET was not genotoxic in a battery of in vitro genotoxicity studies, which included a bacterial reverse gene mutation assay, a chromosome aberration assay, a mammalian gene mutation assay, as well as an unscheduled DNA synthesis assay. In a published study, the genotoxic potential of DEET was assessed in an in vitro comet assay in primary human nasal mucosal cells obtained from biopsies. In this study, DEET was found to increase DNA damage in a dose-dependent manner. However, there were several limitations identified in this study, including the fact that there was no indication of the reason the nasal biopsies were obtained, or why patients underwent nasal surgery, leading to uncertainty regarding whether the samples were from healthy nasal tissue. An in vivo micronucleus assay was not available; however, given the negative findings in the battery of in vitro genotoxicity studies and the lack of tumorigenicity observed following chronic exposure in the long-term studies with two rodent species, the weight of evidence indicates a low concern for any uncertainties that could arise from the lack of this in vivo genotoxicity study.

In the available rat and rabbit developmental toxicity studies, there was no evidence of treatment-related fetal malformations or sensitivity of the young. In the rat gavage developmental toxicity study, decreased fetal weight was noted at maternally toxic dose levels, with maternal effects consisting of mortality, clinical signs of toxicity and decreased body weight gain and food consumption. In the rabbit gavage developmental toxicity study, delayed ossification in some interphalanges and an increased incidence of rudimentary ribs on the thoracic arch were noted in the presence of maternal toxicity, characterized by a decrease in body weight, body weight gain, and food consumption.

In a dietary 2-generation reproductive toxicity study in rats, there was no evidence of sensitivity of the young, reproductive toxicity, or adverse effects in the endocrine tissues assessed noted up to the highest dose tested. In parental animals, kidney effects were observed in males; however, as noted previously, these findings were not considered relevant for the human health hazard assessment. Additionally, reduced body weight during the pre-mating period and decreased food consumption were noted in parental animals at the highest dose tested. In offspring, a decrease in pup body weight (5.0 and 6.8% relative to control values in males and females, respectively) was observed at the mid-dose level on postnatal day (PND) 21 but only in the second filial (F2) generation. At this stage of the weaning period, pups are exposed to the test substance through both milk and feed, likely resulting in an increased level of exposure which confounds the interpretation of the body weight findings. Given that offspring test substance intakes during this period were likely much higher than the external maternal doses used to establish the effect levels in this study, it was not considered appropriate to establish the offspring lowest-observed-adverse-effect level (LOAEL) based on the isolated decrease in pup body weight on PND 21 at the mid-dose level. No other treatment-related effects were observed in offspring at the mid-dose level at any time-point in this study. At the high-dose level, a significant reduction in body weight was observed in F1 and F2 offspring throughout most of the lactation period, and the offspring LOAEL was established at the high dose based on this finding.

Overall, the developmental and reproductive toxicity studies did not provide evidence of increased sensitivity of the young when compared to the adult animal. However, these studies were conducted according to test guidelines available at the time and they do not reflect all current test guideline requirements, which includes a longer dosing period in the developmental toxicity studies and a more robust assessment of endocrine-sensitive and reproductive endpoints in the reproductive toxicity studies. Given the limitations identified with these studies, the registrant-submitted studies and information from the published scientific literature were considered in the overall weight of evidence for the potential of DEET to have an impact on the mammalian endocrine system.

In vitro data from the USEPA ToxCast pathway models for androgen and estrogen, as well as the consensus Estrogen Receptor Quantitative Structure-Activity Relationship models (ER QSAR; from the Collaborative Estrogen Receptor Activity Prediction Project [CERAPP][5]) and Collaborative Modeling Project for Androgen Receptor Activity (CoMPARA Androgen Receptor Quantitative Structure-Activity Relationship [AR QSAR][6]) models did not predict endocrine bioactivity for DEET.

In the 2-generation reproductive toxicity study, although several endocrine-sensitive endpoints required by the current OECD test guideline were not assessed, including estrous cyclicity, sperm parameters and effects on sexual maturation, histopathological evaluations were conducted on the ovaries, prostate, seminal vesicles, testes with epididymis, uterus, and vagina, and testes were weighed, and no treatment-related findings were identified.

In other studies in the toxicology database, effects on ovary weight were reported in rats, hamsters and dogs following short-term dietary administration of DEET; however, these changes occurred at dose levels above the limit dose of testing in the presence of significant systemic toxicity in hamsters and rats or were not replicated in similar studies in dogs via capsule administration, which tempers concern for these findings. Furthermore, no histopathological findings were noted in the ovary in these studies, in the 2-generation reproductive toxicity study, or following extended dosing in the long-term rat and mouse dietary toxicity studies. Alterations in testes weight were also reported in several toxicity studies with increased weights noted in the 90-day dermal toxicity study in micropigs and in the 24-month oral toxicity study in rats; however, these changes were not associated with any histopathological findings, and were not deemed adverse. Decreases in testes weight were noted following short-term oral administration in hamsters and dogs; however, concern for these findings was tempered by the presence of significant systemic toxicity in both species at the same dose level and the lack of similar findings in dogs following a longer dosing period. Additionally, testes weights were not affected in the 2-generation reproductive toxicity study.

[5] Mansouri, K. et al., 2016. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. Environ Health Perspect.; 124(7):1023-33.

[6] Mansouri, K. et al., 2020. CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity. Environ Health Perspect.; 128(2): 27002.

Further, the effect of DEET on spermatogenesis was examined in a non-guideline 9-week dermal toxicity study in the rat. In this study, no treatment-related effects on sperm count, sperm viability or morphology were noted and no microscopic testicular lesions were observed. Endocrine-sensitive tissues, including the ovary, testes, uterus, pituitary, thyroid and adrenal gland, were examined in the 90-day dermal rat toxicity study, and there were no treatment-related effects observed.

The association between DEET exposure and adverse reproductive and developmental outcomes in the human population was examined in several published epidemiological studies. As further discussed below, although the utility of these studies in the hazard assessment was hampered due to identified limitations in exposure ascertainment, they were not found to show any clear associations between DEET exposure and adverse reproductive outcomes.

Based on the overall weight of evidence, there is low concern for the potential impact of DEET on endocrine-sensitive tissues. The shorter dosing duration in the developmental toxicity studies and the absence of measurements of certain endocrine-related endpoints in the 2-generation reproductive toxicity study were not considered to significantly impact the hazard characterization of DEET given the absence of particular concerns for these endpoints when considering the entirety of the available toxicology database.

The neurotoxic potential of DEET was investigated in a guideline rat acute neurotoxicity study and a non-guideline repeat-dose neurotoxicity study in rats, in which F2 pups obtained from the 2-generation reproductive toxicity study were exposed to DEET via the diet for an additional 9-month period before undergoing a neurotoxicity assessment that included a functional observation battery and assessments of motor activity, acoustic startle response, and learning and memory (water maze and passive avoidance tests), as well as a neuropathological examination.

In the rat acute gavage neurotoxicity study, mid- and high-dose animals exhibited increased vocalizations at both one and 24 hours post-dosing. Additionally, increased piloerection and tremors were observed in high-dose animals at these timepoints. To refine the interpretation of the thermal pain response and motor activity data, Health Canada conducted statistical modeling for these data. A linear regression model was used to assess the response time following a painful thermal stimulus across dose groups. In the absence of a statistically significant treatment-by-sex interaction, the data from both sexes were combined to increase statistical power of the analysis.[6] Due to the large variability observed in the data, the impact of outliers was also considered. Based on this analysis, the increased response times to painful thermal stimuli noted in the mid- and high-dose groups at one hour post-dosing, and in the high-dose group at 24 hours post-dosing were attributed to treatment. For the motor activity data, Health Canada employed a linear mixed-effects model to assess the data from four key measurements: vertical activity, horizontal activity, total distance, and movement time. As noted previously, in the absence of a statistically significant treatment-by-sex interaction, the data from both sexes were combined to increase statistical power of the analysis.[7] The analysis indicated a statistically significant decrease in vertical activity in the mid- and high-dose groups and in horizontal

[7] Holson, R. Robert, et al., 2008. Statistical issues and techniques appropriate for developmental neurotoxicity testing: a report from the ILSI Research Foundation/Risk Science Institute expert working group on neurodevelopmental endpoints. *Neurotoxicology and teratology;* 30.4: 326-348.

activity and movement time in high-dose animals one hour post-dosing. These decreases in motor activity were considered to be related to treatment. All treatment-related effects were resolved within two weeks and there was no treatment-related effect on neuropathology.

In the non-guideline repeat-dose dietary neurotoxicity study that used F2 pups from the reproductive toxicity study, systemic toxicity, characterized by decreases in body weight, was observed in all treated female groups, and in males at the mid- and high-dose levels. Despite some procedural and reporting limitations, the neurotoxicity assessment, which included a functional observational battery, as well as assessment of motor activity, passive avoidance, and acoustic startle response, was considered adequate to assess the neurotoxic potential of DEET following in utero and repeated exposure. For the assessment of the motor activity findings, a linear mixed-effects model was used to assess the data from four key measures: vertical activity, horizontal activity, total distance, and movement time. Based on this analysis, statistically significant increases in horizontal activity and total distance were noted in high-dose females, which were considered related to treatment. No other treatment-related findings were observed in the neurotoxicity assessment and no treatment-related neuropathological findings were noted in this study.

Several studies investigating the neurotoxic potential of DEET were identified in the published scientific literature. In a rat 30-day dermal neurotoxicity study (PMRA No. 3225516) that examined effects on motor function, including locomotor activity, mobility and agility, no treatment-related effects were reported. Furthermore, the in vitro neurocellular experiments conducted in parallel in this study concluded that DEET affected neuron viability only after a prolonged exposure period and had no impact on astrocyte viability. Several in vitro studies demonstrated the potential for DEET to inhibit mammalian and insect acetylcholinesterase (AChE) activity (PMRA No. 3607698, PMRA No. 3248574) as well as butyrylcholinesterase (BuChE) activity (PMRA No. 3248567). Additionally, computational molecular docking studies indicated that DEET had the potential to bind to the human AChE active sites (PMRA No. 3248567). AChE activity inhibition by DEET was reported to be reversible and to occur at relatively high in vitro concentrations in these studies. Although some limitations were identified, overall, these studies indicated that DEET has low potency for inhibiting AChE activity, and is thus unlikely to cause toxicity by this mechanism in humans. The lack of findings consistent with cholinergic toxicity in the available mammalian toxicology database further supports this conclusion.

A guideline developmental neurotoxicity study conducted with DEET, which would have assessed the potential for neurotoxicity in young animals following exposure during gestation and lactation, was not available. However, in the non-guideline repeat-dose neurotoxicity study, F2 rat offspring from the 2-generation reproductive toxicity were assessed for evidence of neurotoxicity following exposure in utero and extended dosing throughout development and adulthood. In this study, evidence of neurotoxicity was limited to alterations in motor activity which occurred in the presence of significant systemic toxicity and at dose levels higher than those causing alterations in motor activity following acute exposure in adult rats. Moreover, published in vitro and in vivo scientific information does not raise any concern for the developmental neurotoxic potential of DEET. As further discussed below, the association between DEET exposure and neurodevelopmental outcomes was examined in a cross-sectional

epidemiological study, which despite limitations in exposure ascertainment, did not show any evidence of associations with adverse neurodevelopmental outcomes in humans. Overall, the available toxicology database is considered sufficient to assess the neurotoxic potential of DEET.

The toxicology reference values for the human health risk assessment are summarized in Appendix III, Table 1. The results of toxicology studies conducted on laboratory animals with DEET are reported in Appendix III, Table 2.

Epidemiology

Numerous epidemiology studies were identified in the published scientific literature that explored associations between DEET exposure or use in human populations and various potential health outcomes, including reproductive and developmental outcomes, cardiovascular disease, and obesity. The majority of the studies identified in the literature were cross-sectional studies, which are inherently limited in their ability to determine causal relationships. Various limitations, including the lack of adequate exposure characterization, were also noted in these studies and are further discussed below.

Reproductive and developmental outcomes

The association between DEET exposure and sperm parameters was examined in a case control study that measured urinary concentrations of DEET (PMRA No. 3607714) and in a cross-sectional study (PMRA No. 3607706) that measured urinary concentrations of DEET and the metabolites DCBA and DHMB. No association between DEET exposure and decreased semen quality was reported by the authors in either study. A case control study was conducted to examine the association between pesticide exposure, including DEET, during pregnancy and holoprosencephaly (PMRA No. 3607739). In this study, the use of DEET during the preconception period was reported by study authors to be associated with increased risk for holoprosencephaly in an unadjusted model (odds ratio [OR] = 8.58; 95% confidence interval [CI]: 1.03–185.33); however, no significant association was reported for exposure during pregnancy and the confidence interval for the OR during preconception was very wide, indicating low certainty with the results. This study was considered to be of limited relevance for hazard characterization due to significant design limitations. More specifically, exposure ascertainment was based on self-reported questionnaire data rather than biological measurements, rendering it susceptible to recall bias. Furthermore, differences in case and control group characteristics during and after selection may have introduced bias or unmeasured confounding factors which could not be adjusted for by the authors due to the study's small sample size.

The relationship between pesticide concentrations in maternal and/or cord blood and adverse birth outcomes such as birth weight, birth length, and abdominal and head circumferences was investigated in a prospective cohort study (PMRA No. 3607721) and in a cross-sectional study (PMRA No. 3607719). No association between maternal and/or cord blood DEET concentrations and adverse birth outcomes were reported in either study. A cross-sectional study examining the association between DEET exposure, as measured by urinary concentrations of DCBA and

EACB[8], and neurobehavioral performance in Ecuadorian adolescents (PMRA No. 3607699) was also identified. No association between urinary concentration of DEET metabolites and impaired neurobehavioral performance was reported by the authors in this study. Overall, there was insufficient evidence to support an association between DEET exposure and the reproductive or developmental outcomes examined.

Cardiovascular disease, obesity and other adverse health outcomes

Several studies were identified in the published literature which investigated the association between DEET exposure and obesity, cardiovascular disease, and other health outcomes. A cross-sectional study used data from 8770 individuals participating in the National Health and Nutrition Examination Survey (NHANES) to examine associations between DEET exposure, as measured by urinary concentrations of DCBA, and general obesity (based on body mass index) and abdominal obesity (based on waist circumference) in the general adult population (PMRA No. 3607730). Participants were grouped into tertiles based on their urinary DCBA levels, with the lowest tertile serving as the reference group. Study authors reported that higher urinary DCBA concentrations were positively associated with the prevalence of obesity. Specifically, the odds ratios for general obesity were 1.18 (CI: 0.97-1.44) for the second tertile and 1.36 (CI: 1.15-1.61) for the third tertile. For abdominal obesity, the ORs were 1.22 (CI: 1.02-1.44) and 1.28 (CI: 1.08–1.54) for the second and third tertiles, respectively.

In a prospective cohort study that used NHANES data from 2199 adults (aged 60 years and above; PMRA No. 3607732), study authors reported that higher DEET urinary concentrations were associated with a higher risk of incident cardiovascular death after adjusting for key confounders (hazard ratio [HR] = 1.97; CI: 1.14–3.40; $P<0.05$). However, similar associations were not reported in this study for the urinary DEET metabolites DCBA (HR = 1.22; CI: 0.97–1.16) or DHMB (HR = 1.31; CI: 0.94-1.85). Confidence in this reported association with urinary levels of DEET is limited due to its rapid metabolic conversion in humans and the lack of similar associations with the DEET metabolites measured in this study, which are more extensively detected in urine.

A cross-sectional study using NHANES data from 5972 adults examined the association of DEET exposure, as measured by urinary concentrations of DEET, DCBA and DHMB, and "total" and specific cardiovascular disease (PMRA No. 3607701). Total cardiovascular disease was defined as an individual self-reporting they had been diagnosed with any of the following specific outcomes: congestive heart failure, coronary heart disease, angina, heart attack, or stroke. The study authors reported an association between higher urinary DCBA levels and increased risks of "total" (or any) cardiovascular disease and coronary heart disease, after adjusting for confounders. The OR for "total" cardiovascular disease was 1.32 (CI: 1.03–1.68), and 1.57 (CI: 1.10–2.25) for coronary heart disease. However, no associations were reported in the study between DCBA levels and heart attack, congestive heart failure, angina, or stroke. The study authors noted that the reported associations between DEET exposure and cardiovascular disease in this study should be interpreted with caution given that other confounders such genetic factors may have impacted the prevalence of this health outcome and should be explored further.

[8] Referred to in the published study report as ECBA.

They also cautioned that self-reporting of cardiovascular outcomes in this study may have led to misclassifications of outcomes for some participants. It is noteworthy that there was no evidence of effects on the cardiovascular system identified in the DEET animal toxicology database.

In a separate cross-sectional study, the study authors explored the association between urinary concentration of DCBA and the likelihood of having kidney stones in the U.S. population (PMRA No. 3607712). Data from a total of 7567 NHANES participants (from 2007–2016) were analyzed, and the study authors reported a positive association between higher DCBA urinary concentrations and the odds of kidney stones, with an OR of 1.36 (CI: 1.08–1.72). An additional cross-sectional study investigated the association between urinary DCBA levels and hyperuricemia using data from 8708 NHANES participants from 2007–2016 (PMRA No. 3607726). A positive association was reported between the prevalence of hyperuricemia and DCBA levels, with an OR of 1.41 (CI: 1.14–1.74). Another cross-sectional study examined associations between several health biomarkers, including kidney function (estimated glomerular filtration rate), and exposure to DEET, as measured by urinary concentrations of the metabolite EACB.[9] The study authors did not find a significant correlation between the DEET metabolite and kidney function (PMRA No. 3607707). Similarly, there were no associations reported between DEET exposure and the other biomarkers examined, which included those related to systemic inflammation, and immune and liver function.

For all of the studies discussed in this section, reliance on a single biomonitoring measurement to characterize chronic exposure introduces uncertainty, as such measurements may not accurately reflect long-term exposure given the rapid elimination of DEET. Overall, there is no clear evidence to support an association between DEET exposure and the cardiovascular, obesity or other adverse health outcomes examined in these studies.

Conclusions regarding epidemiological studies

All of the identified epidemiological studies were deemed to lack adequate exposure characterization. Although many of these studies included human biomonitoring data, reliance on a single biological measurement to reflect repeated or chronic exposure was considered problematic due to the rapid elimination of DEET and its metabolites (which have a half-life of approximately 7 hours). These factors limited their utility in informing the hazard assessment. Overall, the epidemiological data did not provide evidence of a clear associative or causal relationship between exposure to DEET and the adverse health effects examined. While epidemiological data have inherent limitations, and are typically designed to look for associations, rather than causes, they have value and their reported findings can have the advantage of being directly based on human exposures and population responses. Health Canada uses these studies in different evaluation scenarios where they are considered alongside toxicity studies which examine toxic effects over various dose levels, and continues to support the conduct of well-designed epidemiological studies where exposure conditions are well characterized.

[9] Referred to in the published study report as 3-(ethylcarbamoyl) benzoic acid (ECBA), a synonym for EACB (PMRA No. 3607707).

3.1.1 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.[10]

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies, including gavage developmental toxicity studies in rats and rabbits, and a dietary 2-generation reproductive toxicity in rats. While these studies were conducted according to older test guidelines and are not completely compliant with modern standards, the concern for any limitations in the protocol or assessments was low, and the studies were considered adequate to characterize the potential reproductive and developmental toxicity of DEET. A non-guideline repeat-dose neurotoxicity study in rats, in which F2 pups obtained from the 2-generation reproductive toxicity study were exposed to DEET via the diet for an additional 9-month maintenance period before undergoing a neurotoxicity assessment, was also available.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of offspring compared to parental animals in the rat dietary 2-generation reproductive toxicity or in the gavage prenatal developmental toxicity studies in rats and rabbits. In the 2-generation reproductive toxicity study, reduced body weights were observed in offspring at the high-dose level in the presence of parental effects in the form of reduced body weights, body weight gains, and food consumption. As noted above, a decrease in body weight was also observed at the mid-dose level in F2 pups at the end of lactation period where pups were likely exposed to the test substance through both milk and feed, confounding the interpretation of the finding. Given that offspring test substance intakes during this period were likely much higher than the external maternal doses used to establish the effect levels in this study, it was not considered appropriate to establish the offspring LOAEL based on the isolated decrease in pup body weight on PND 21. In the rat developmental toxicity study, decreased fetal weight was noted at a dose level that resulted in increased mortality, reduced body weight gain, and clinical signs of toxicity in maternal animals. In the rabbit developmental toxicity study, delayed ossification in some interphalanges and an increased incidence of skeletal variations were observed at a dose level associated with reduced body weight and food consumption in maternal animals. In the non-guideline repeat-dose neurotoxicity study, there was no indication of increased sensitivity to neurotoxic effects of rat offspring following prenatal exposure and prolonged dosing into adulthood since effects on motor activity were noted at the highest dose tested only, a dose that was associated with effects on body weight and food consumption in parental animals.

[10] SPN2008-01, The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

Overall, the database is adequate for determining the potential sensitivity of the young. Effects noted in the young were well-characterized and occurred in the presence of maternal toxicity. On the basis of this information, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold for all scenarios.

3.2 Dietary exposure and risk assessment

There are no food uses associated with the use of DEET. Residues of DEET in potential drinking water sources are not anticipated as a result of the insect repellent use. Therefore, no dietary exposure is anticipated.

3.2.1 Determination of acute reference dose (ARfD)

Establishment of an acute reference dose is not required as no exposure via the diet or drinking water is expected.

3.2.2 Determination of acceptable daily intake (ADI)

Establishment of an acceptable daily dose is not required as no exposure via the diet or drinking water is expected.

3.3 Occupational and non-occupational exposure and risk assessment

Occupational and non-occupational (residential) risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.3.1 Toxicological reference values for non-occupational exposure

3.3.1.1 Acute incidental oral

For the assessment of acute non-dietary (incidental) oral exposure to children, the NOAEL of 50 mg/kg bw from the acute gavage neurotoxicity study in the rat was selected. At the LOAEL of 250 mg/kg bw, decreased motor activity and increased response time following thermal stimuli were observed in both sexes, and increased vocalization was observed in males.

The target margin of exposure (MOE) for this scenario is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed in the *Pest Control Products Act* hazard characterization Section, the PCPA factor was reduced to onefold.

3.3.1.2 Short- and intermediate-term dermal exposure

For the short- and intermediate-term non-occupational dermal risk assessment, the NOAEL of 300 mg/kg bw/day from the 90-day dermal toxicity study in the rat was selected. This study was conducted via the relevant route and was of an appropriate duration. At the LOAEL of 1000 mg/kg bw/day, decreased body weight gain and kidney effects were observed in both sexes, and decreased body weight and food efficiency were also noted in males.

The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed in the *Pest Control Products Act* hazard characterization Section, the PCPA factor was reduced to onefold. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

3.3.1.3 Cancer assessment

There was no evidence of tumourigenicity, and therefore, a cancer risk assessment is not necessary.

3.3.2 Residential exposure and risk assessment

There is potential for exposure to DEET for the general public using ready-to-use domestic-class products as a personal insect repellent. Exposure is expected to be predominantly dermal as DEET is applied directly to the skin. Based on the registered use pattern, dermal exposure is expected to range from short- to intermediate-term in duration, depending on the sub-population. Inhalation exposure is expected to be minimal relative to the dermal route as products are expected to be applied while outdoors and not directly on the face. There is also potential for acute/episodic incidental oral exposure for children (1<2 years old).

A highly refined human health exposure and risk assessment was conducted as part of the previous re-evaluation (RRD2002-01) using a large database of chemical-specific pharmacokinetic, dermal absorption and use information. Use information included a usage study that involved over 540 men, women, and children at three different locations in the United States. There was extensive consultation on the risk assessment approach, including a scientific advisory panel consisting of 5 representatives of the Canadian Pediatric Society and a Health Canada representative of the Bureau of Pharmaceutical Assessment.

Continued registration of DEET was determined to be acceptable at that time provided that mitigation measures were implemented. These mitigation measures included discontinuation of domestic-class products containing more than 30% DEET, discontinuation of combination products containing both DEET and sunscreen, as well as reducing the concentration of DEET in products and number of applications for young children. These mitigation measures were implemented and remain part of the current conditions of use for domestic-class products:

- Products containing DEET cannot be used on children less than 6 months of age.
- Products containing 10% or less DEET can be applied to children between 6 months to 12 years old as follows:

- Only one application per day for children 6 months to 2 year olds. No more than 3 applications per day for children 2 to 12 years old.
- Avoid application to the hands.
- Not for daily use.

- Products containing 30% or less DEET can be used on adults and youth (children> 12 years of age).
- The minimum re-application interval is 2–8 hrs, depending on the concentration of DEET (application interval increases with the concentration).
  Aerosol cans and pump products are not to be sprayed in enclosed spaces.

As a result of the previous re-evaluation, Health Canada concluded that risks and the continued registration of DEET were acceptable provided that mitigation measures were implemented. These mitigation measures were implemented and remain part of the currently registered use pattern for domestic-class products.

Dermal exposure and risk assessment

The previous dermal exposure and risk assessment continues to be appropriate to assess the current use pattern of DEET products, as the previous assessment was highly refined based on chemical-specific data and addresses the generic input parameters from the USEPA Residential SOPs (2012). The chemical-specific data used previously included a large usage survey that provided information on the amount of DEET applied per person per application. This usage information continues to be the best data available and is used by other international regulatory agencies to characterize exposure. No usage data of similar quality have been submitted to Health Canada or are available in the literature.

As there were no changes to the dermal toxicology reference value or the exposure assessment, the previous risk assessment continues to be reflective of the current use pattern. Dermal risks were shown to be acceptable for the currently registered use pattern for domestic-class products. The acceptability of the health risks related to the currently registered use pattern was verified using the real-world Canadian biological monitoring study, discussed in greater detail below in Section 3.3.2.1.

As a result, no additional risk mitigation measures, beyond what is currently on the label, are proposed.

Incidental oral exposure and risk assessment

Incidental oral exposure of DEET from hand-to-mouth transfer is expected to be episodic (acute) and not a significant route of exposure due to the smell and taste of DEET, which acts as a self-deterrent against hand-to-mouth transfer. In the previous re-evaluation, potential incidental oral exposure was modelled using generic inputs consistent with the models of the time. As these models have been updated in the USEPA 2012 Residential SOPs, the acute incidental oral assessment was quantitatively updated in this re-evaluation.

The incidental oral exposure model is considered to be conservative for DEET, as products are not to be applied directly to children's hands. In addition, fewer mouthing events are expected than were modelled due to the smell and taste (palatability) of DEET.

The results of the incidental oral exposure and risk assessment are shown in Appendix IV, Table 1. Calculated MOEs were greater than the target MOE and risks were shown to be acceptable. As incidental oral risks were acceptable for the currently registered use pattern for domestic-class products, no additional mitigation measures, beyond what is currently on the label, are proposed.

3.4 Aggregate exposure and risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). No exposure to DEET via the diet or drinking water is expected. Further, since incidental oral exposure is episodic (acute) it was not combined with the short- to intermediate-term dermal exposure. Therefore, a standard aggregate risk assessment is not required.

3.4.1 Residential aggregate exposure and risk assessment using human biological monitoring data

Biological monitoring or biomonitoring is a method of assessing exposure to a pesticide by measuring the pesticide or its metabolites in biological media, such as urine or blood. Compared to ambient monitoring, biological monitoring provides an integrated estimate of exposure through all potential routes (inhalation, dermal and oral) and by all possible pathways (for example, food, drinking water and indoor uses) and better reflects behavioural and physical sources of variability. In the case of DEET, exposure is expected to be almost entirely through the dermal route as it is applied directly to the skin. Potential minor exposure through other routes (inhalation, oral) will also be captured in the biomonitoring data. Use of biomonitoring data differs from the standard approach for aggregate human health risk assessments, in which exposure models and algorithms are used to estimate route-specific exposures using measurements of pesticide concentrations in the environment or what is deposited on the skin, inhaled, and/or consumed for specific scenarios.

Assessments conducted with human biomonitoring (HBM) data are considered to be refined since biomonitoring data are reflective of the "real-life" use of chemicals and all relevant exposure routes and pathways. Therefore, HBM data may be used when evaluating aggregate exposure to a pesticide to support risk estimates generated using Health Canada's standard approach for pesticide human health risk assessments.

After DEET is applied to the skin, a small amount can be absorbed through the skin. Once absorbed, it is rapidly broken down in the body to form metabolites or excreted unchanged in the urine. The main metabolite is DCBA. A minor metabolite commonly included in biomonitoring studies is DHMB. DEET and its metabolites can be measured in urine, and are reflective of relatively recent exposure.

HBM data from the Canadian Health Measures Survey (CHMS; cycles 4 and 6; 2007–2011) and a targeted population biomonitoring study conducted by Health Canada were considered in the DEET re-evaluation.

The CHMS is an on-going, nationally representative health measures survey that has been conducted by Statistics Canada, in partnership with Health Canada and the Public Health Agency of Canada, since 2007. The cross-sectional survey collects information from people living in Canada such as physical measures (for example, height and weight) and general health (for example, blood pressure and fitness), as well as a biomonitoring component through which over 300 environmental chemicals have been measured. It follows a similar study design to the U.S. NHANES. In Cycle 1 of the CHMS (2007–2009), blood and spot urine samples were collected from approximately 5600 Canadians, 6–79 years old. In subsequent cycles, data was collected from approximately 5700 to 6400 Canadians per cycle aged 3–79 at 16–18 sites across Canada. DEET and DEET metabolites (DCBA and DHMB) were included in the suite of compounds measured. In the general population (3–79 years), DEET was detected in ≤ 2% of the samples and a geometric mean could not be determined due to the low number of detections. DCBA was detected more frequently (up to 89% of samples) in the general population (3–79 years) with geometric mean concentrations that ranged from 2.1 to 5.6 µg/L.

An observational, targeted biomonitoring study was conducted by Health Canada in 2019 at three summer camps in Ontario. The study was approved by the Health Canada Research Ethics Board. In this study, Canadian children (7 to 13 years old) used Health Canada-approved DEET-based repellents as they normally would in an overnight camp setting. Products were formulated as spray cans, spray pumps, or lotions. For a 24-hour monitoring period, children provided multiple spot urine samples and reported information about their use of DEET and camp activities, including factors (such as bathing) which could influence absorption of DEET. The estimated amount of DEET applied by each child was determined from weighing the containers before and after the monitoring period. DEET and two metabolites, DHMB and DCBA, were measured in collected urine samples. As urinary concentrations varied with the amount of time since the last application as well as with the amount of DEET applied (low, medium, upper), results were reported considering each of these factors. Results of these analyses were included in the dose reconstruction (reverse dosimetry) analysis, as further discussed below. Due to unreliable quality control sample recoveries, results for DHMB were not reported in the study. Geometric mean concentrations of DEET ranged from 8.4 to 12.4 µg/L for samples collected between 2 and 28 hours after the last DEET application, and 5.8 to 30.9 µg/L for samples collected from children who had low to upper estimated DEET exposure during the monitoring period. Geometric mean concentrations of DCBA were greater than those measured for DEET and ranged from 12 000 to 16 600 µg/L for samples collected between 2 and 28 hours after the last DEET application, and 6800 to 41 000 µg/L for samples collected from children who had low to upper estimated DEET exposure during the monitoring period.

The Health Canada targeted biomonitoring study was considered to be the best data available to estimate exposure from using registered domestic-class DEET products. Levels in this study are greater than those reported in CHMS, which is expected as DEET and metabolites are rapidly excreted in urine following exposure and the CHMS sampled population would include both people who have recently applied DEET and those who have not. Although the targeted

biomonitoring study only included children, the exposures estimated from the study were considered to address other sub-populations (in other words, ages) and exposure scenarios as the study was conducted in a high pest pressure environment, the majority of children did not wash or shower during the monitoring time, and children have a higher surface area to body weight ratio compared to adults. In addition, it was assumed that all metabolite levels measured in urine were due to exposure from a single day. This is a conservative assumption as the monitoring period took place on the 2nd day of camp or later and applications of DEET prior to the monitoring period would have contributed to the urine concentrations measured on the monitoring day. Assuming all measured metabolites are from DEET products applied in a single day results in a higher calculated daily exposure than what was occurring in the study.

While biological screening levels (biomonitoring equivalents) are available for DEET and the metabolite DCBA, a refined reverse dosimetry approach (exposure reconstruction) was used in the re-evaluation as the full biomonitoring study dataset was available and it was possible to conduct the assessment with the specific parameters from the monitored population. Reverse dosimetry is an approach that can be used to convert metabolite measurements in humans to an estimate of human pesticide exposure (mg/kg bw/day) using human pharmacokinetic data. The human pesticide exposure estimates are then compared to toxicological reference values to estimate risk.

Published and unpublished literature studies on the pharmacokinetics of DEET in humans were available and considered in the approach for interpreting biomonitoring data in a risk assessment context. Most of these were dermal administration studies, which reflect the use of DEET in domestic-class products. Proportions of absorbed DEET excreted as the main metabolite, DCBA, in the urine (urinary excretion fraction) were determined for adults and children from these studies. A “fraction of administered dose absorbed” value was also determined from the studies and used to convert the estimated absorbed dose into an estimate of dermal (administered) DEET. This conversion was required so that the final estimated exposure could be compared with the toxicology reference value determined from a rat dermal toxicity study.

The results of the residential aggregate risk assessment using biomonitoring data are shown in Appendix IV, Tables 2 and 3. Calculated MOEs considering the amount of DEET applied (low, medium, upper) and time since the last application were greater than the target MOE and risks were shown to be acceptable for registered Canadian domestic-class products with current mitigation measures. This outcome is consistent with and supports the outcome for the standard risk assessment approach (Section 3.3.2). As a result, no additional risk mitigation measures, beyond what is currently on the label, are proposed. In addition to the conservatisms in the biomonitoring data discussed above, there are conservatisms in the risk assessment. For example, the modelled risk assumes that human skin is as permeable to DEET as rat skin. However, dermal absorption of DEET in humans is lower than in rats).

3.4.2 Occupational exposure and risk assessment

There are currently no registered commercial-class products containing DEET. Exposure for occupational workers handling domestic-class products is addressed by the domestic-class product risk assessment.

3.5 Cumulative assessment

The *Pest Control Products Act* requires that Health Canada consider the cumulative effects of pest control products that have a common mechanism of mammalian toxicity. A Science Policy Note (SPN2018-02) entitled Cumulative Health Risk Assessment Framework[11] describes the framework and methodology that Health Canada's PMRA uses for assessing the cumulative health effects of pesticides. Consistent with the approach outlined in SPN2018-02, Health Canada followed a weight-of-evidence approach to explore the potential for a common mechanism of mammalian toxicity for this active ingredient with other pesticides. Health Canada considered chemicals within the same class of pesticides, which takes into consideration similarities with respect to structure and pesticidal mode of action. DEET is a member of the N,N-dialkylamide class of chemicals. No other pesticides in the same class of chemicals were identified and no information was identified to indicate that DEET shares a common mechanism of toxicity with other pest control products. Therefore, a cumulative health risk assessment is not required at this time.

3.6 Health incident reports

As of 22 May 2025, 268 human and 29 domestic animal incidents involving DEET were submitted to Health Canada.

Overall, most human incidents (220 reports) were considered to be related to the reported DEET product. The remaining human incidents (48 reports) could not be linked to the reported DEET product. The majority of the incidents related to the reported DEET product involved products containing ≥ 15% DEET (63% of all human incidents) followed by products containing ≤ 10% DEET. The products were mainly formulated as pressurized sprays or pump sprays. DEET incidents frequently involved adults (or individuals >12 years of age) (68% of all individuals) whereas children (between >1 to 12 years of age) made-up nearly a third of all reported incidents. The commonly reported exposure scenarios, in adults and children, included accidental exposure to DEET during product application as well as inhaling DEET during product use. The severity of effects reported in children and adults were mainly minor. There was a fairly high degree of association between the symptoms reported in people and exposure to a DEET insect repellant. Direct exposure to the DEET product, either via the skin or eye, was reported in most incidents resulting in either skin or eye irritation shortly after exposure, as well as the occurrence of mild respiratory or general reactions (for example., headache or nausea) soon after product application. In some incidents (30 incidents including 1 major U.S. incident), the individual reported receiving medical treatment for shortness of breath, hypoxia, throat swelling or irritated skin.

Other reported incidents involved individuals using DEET products in close proximity to synthetic surfaces and reporting peeling surfaces, property damage or minor injury (7 incidents). In addition, there were reports of individuals applying DEET products near an open flame resulting in treated areas catching on fire and resulting in more serious effects such as 2nd or 3rd degree burns, hair loss or sensory abnormalities (5 incidents including 2 major incidents, one

[11] Science Policy Note SPN2018-02, *Cumulative Health Risk Assessment Framework* - Canada.ca

of the 2 major incidents occurred in Canada). The DEET products reported in these incidents contained label statements informing the consumer that the product may damage furniture finishes, plastics and painted surfaces or to keep the product away from an open flame or spark, as appropriate.

In addition to the human incidents, there were a few domestic animal incidents (13 reports) related to the reported DEET products. The incidents mainly involved dogs. The animal exposure scenarios reported in incidents included people applying DEET products to their pets, pets licking treated areas (for example, treated skin of owners) or pets biting into DEET products. The remaining animal incidents (16 reports) could not be linked to the reported DEET product.

The overall number of Canadian human and domestic animal incidents involving DEET is relatively low when compared to the high volume of use of DEET products in Canada. Additionally, no significant health concerns were identified following the evaluation of DEET incidents. Nevertheless, DEET label improvements are recommended to clarify existing precautionary and use direction statements required on registered products and to help reduce incidents related to the inappropriate use of DEET insect repellant products. Additionally, the precautionary statement "skin reactions (for example, itchy skin, rash) may occur in rare cases" is recommended to inform users of the potential minor adverse skin reactions that were observed in some of the incident reports, which may occur following use of DEET products in rare instances.

These label improvement statements are detailed in Appendix VI.

4.0 Environmental assessment

4.1 Fate and behaviour in the environment

DEET is relatively water soluble and stable to hydrolysis. Although biotransformation dissipation rates in water are not available, DEET is expected to be susceptible to transformation by bacteria and other microbes. Therefore, DEET is not expected to persist in the environment. Based on a log K_{ow} of 2.02 to 2.4, and bioaccumulation studies (BAF range of 0.8 to 22), DEET is not expected to bioaccumulate in organisms.

Environment and Climate Change Canada (ECCC) provided Health Canada with water monitoring information for DEET which was collected as part of a larger project looking at pharmaceuticals and other human health care products across Canada (PMRA No. 2937040, PMRA No. 2937053, PMRA No. 2937184). The available water monitoring data was limited in the number of samples and geographic location of sampling, with information for only 128 samples being reported. The concentrations reported for Canada (primarily from Ontario, British Columbia, Nova Scotia and Saskatchewan) ranged from 0.00000417 to 0.000923 mg/L. Additional international data were also identified and the values are within the same range as the Canadian data. Only the Canadian data was used in this assessment. Some of the data suggested that there were seasonal trends for presence of DEET in these waterbodies, with peak concentrations being detected in the summer months. The peak concentrations are attributed to the increase in use of the personal insect repellent to deter insects at higher levels of activity,

which primarily occurs during the summer months. The low detections in water, which included samples taken downstream from wastewater treatment plants, are all low. This supports the assumption that this type of use results in minimal environmental exposure and that calculation of exposure estimates for the drinking water component of the dietary risk assessment is not required.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are estimated levels of pesticides in various environmental media, such as food, water, soil and air.

The potential for exposure of non-target organisms in the environment to a personal insect repellent product is expected to be very limited. Aquatic organisms in the environment could be exposed to DEET through wash-off from skin or clothing and entry into surface water bodies through wastewater treatment plants or from people swimming/wading in water. Therefore, aquatic organisms may be exposed to DEET in aquatic systems. Terrestrial organisms are not expected to be exposed to DEET from application as a personal insect repellent.

Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). The values calculated after application of uncertainty factors to the endpoints are labeled effect metrics.

Due to the limited sample size for the water monitoring data, the measured values were only compared to the effect metric and a standard risk assessment was not completed.

4.2.1 Risks to terrestrial organisms

Exposure to terrestrial organisms is not expected based on the current use pattern as a personal insect repellent.

4.2.2 Risks to aquatic organisms

Acute data for algae, *Daphnia* and rainbow trout, and chronic data for daphnia were available in published assessments from the European Union and the USEPA, as well as from published literature. DEET is slightly toxic to practically non-toxic to fish, daphnia, and freshwater algae with endpoints ranging from 75 to 388 mg a.i./L (see Appendix V, Table 1).

Canadian water monitoring data ranged from 0.00000417 to 0.000923 mg/L. After the appropriate uncertainty factor was applied to the aquatic endpoints, the effect metrics were compared to the concentrations reported in water from the monitoring data. The measured water concentrations were several orders of magnitude lower than the effect metrics for all aquatic organisms where data were available.

Therefore, the water monitoring data submitted by ECCC for DEET did not identify a concern for aquatic organisms as all concentrations were well below the effect metrics. The environmental risks associated with DEET, and its associated end-use products, are acceptable when used according to label directions.

4.2.4 Environmental incident reports

As of 10 January 2024, no environmental incident reports involving DEET have been submitted to the PMRA.

4.3 Toxic substances management policy considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, DEET (N,N-diethyl-m-tolulamide) was assessed in accordance with the PMRA Regulatory Directive DIR99-03[12] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that DEET (N,N-diethyl-m-tolulamide) does not meet all of the TSMP Track 1 criteria.

5.0 Value assessment

DEET is used in many domestic class, personal insect repellents and is applied to clothing or directly to skin. DEET is used to repel a number of biting and nuisance insects, including black flies, biting midges, chiggers, deer flies, stable flies, mosquitoes, and ticks. DEET works by reducing detection of users by the insects, thereby reducing the incidence of biting and disease transmission. DEET can repel mosquitoes from 2 to 8 hours, depending upon the guarantee in a product.

[12] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

List of abbreviations

↑	increased
↓	decreased
♀	females
♂	males
µg	microgram
µM	micromole
8-OHdG	8-hydroxy-2'-deoxyguanosine
a.i.	active ingredient
abs	absolute
AChE	acetylcholinesterase
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	androgen receptor
ARfD	acute reference dose
ASR	auditory startle response
AST	aspartate aminotransferase
atm	atmosphere
AUC	area under the curve
BAF	Bioaccumulation Factor
BALC	N,N-diethyl-m-(hydroxymethyl)benzamide
BuChE	Butyrylcholinesterase
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAS	chemical abstracts service
CERAPP	Collaborative Estrogen Receptor Activity Prediction Project
CHMS	Canadian Health Measures Survey
CI	confidence interval
CL_{int}	intrinsic clearance
CoMPARA	Collaborative Modeling Project for Androgen Receptor Activity
CYP	cytochrome P450 enzyme
DCBA	3-diethylcarbamoyl benzoic acid
DEET	N,N-diethyl-m-toluamide
DHMB	*N,N*-diethyl-*m*-(hydroxymethyl)benzamide
DNA	deoxyribonucleic acid
DTU	DEET plus Related Active Toluamides (N, N-diethyl-m-toluamide)
EACB	m-((ethylamino)carbonyl)benzoic acid
EC_{25}	effective concentration on 25% of the population
EC_{50}	half maximal effective concentration which induces a biological response halfway between the baseline and maximum after a specified exposure time
ECBA	3-(ethylcarbamoyl)benzoic acid
ECHA	European Chemicals Agency
EEE	estimated environmental exposure

eNOS	endothelial nitric oxide synthase
ER	estrogen receptor
ESPINA	exposures to Pesticides among Children and Adolescents
ET	N-ethyl-m-toluamide
F1	first filial generation
F2	second filial generation
fc	food consumption
fe	food efficiency
g	gram (s)
GD(s)	gestation day(s)
GSH	glutathione
ha	hectare(s)
HBM	Human Biomonitoring
HCT	hematocrit
HD	high-dose
HGB	hemoglobin
hr(s)	hour(s)
HUVEC	human umbilical venous endothelial cells
IUPAC	International Union of Pure and Applied Chemistry
K	potassium
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram
K_M	Michaelis-Menten constant
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	Litres
LC_{50}	concentration estimated to be lethal to 50% of the test population
LD	lactation day
LD_{50}	dose estimated to be lethal to 50% of the test population
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
MAS	maximum average score for 24, 48 and 72 hours
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
mg	milligram
Min(s)	minute(s)
mL(s)	millilitre(s)
MMAD	mass median aerodynamic diameter
MOE	Margin of Exposure
Na	sodium
NBR	NCI Black Reiter Rat
ng	nanogram
NHANES	National Health and Examination Survey in the United States
NO	nitric oxide
NOAEL	no observed adverse effect level
OECD TG	Organisation for Economic Co-operation and Development Test Guideline
OR	odds ratio

P-generation	parental generation
PCPA	*Pest Control Product Act*
PD	post-dose
pFHHSiD	para-fluorohexahydrosiladiphenidol
PLT	platelet
PMRA	Pest Management Regulatory Agency of Health Canada
PND	postnatal day
ppm	parts per million
RBC	red blood cell
rel	relative
RRD	Re-evaluation Decision Document
SD	Sprague Dawley
SOP	Standard Operating Procedure
tot-bil	Total Bilirubin
USEPA	United States Environmental Protection Agency
VEGF	vascular endothelial growth factor
V_{max}	maximum rate of reaction
wk(s)	week(s)
wt	weight

Appendix I Registered Products Containing DEET in Canada

Table 1 Products containing DEET subject to proposed label amendments[1]

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
18068	Technical grade active ingredient	Aurorium LLC	Deet Insect Repellent	Liquid	98.1%
23785	Technical grade active ingredient	Clariant Corporation	N,N-Diethyl-M-Toluamide	Liquid	98.5%
32282	Manufacturing concentrate	Aurorium LLC	Deet Insect Repellent 30 Bulk	Emulsifiable Concentrate or Emulsion	30.0%
14326	Domestic	The Great Woods, LLC	Great Outdoors Insect Repellent Lotion	Emulsifiable Concentrate or Emulsion	30.0%
15583	Domestic	S. C. Johnson And Son, Limited	OFF! Pump Spray Insect Repellent	Solution	15.0%
20971	Domestic	S. C. Johnson And Son, Limited	OFF! Insect Repellent	Solution	25.0%
21299	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Lotion Insect Repellent For Use On Kids	Emulsifiable Concentrate or Emulsion	7.5%
21411	Domestic	Plz Corp.	K-G Insect Repellent Iv	Pressurized Product	20.0%
21832	Domestic	Plz Corp.	K-G Quick Breaking Insect Repellent Foam I	Pressurized Product	10.0%
21843	Domestic	S. C. Johnson And Son, Limited	OFF! Insect Repellent Pressurized Spray	Pressurized Product	15.0%
22257	Domestic	S. C. Johnson And Son, Limited	Deep Woods OFF! Insect Repellent	Pressurized Product	30.0%
22258	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods Pump Spray Insect Repellent	Solution	25.0%
22611	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Lotion Insect Repellent Family With Aloe Vera	Emulsifiable Concentrate or Emulsion	7.5%
22708	Domestic	S. C. Johnson And Son, Limited	OFF! Active Insect Repellent 1	Pressurized Product	15.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
23099	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Spray Insect Repellent	Solution	7.0%
23487	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods For Sportsmen 1 Insect Repellent	Pressurized Product	30.3%
24368	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Spray Insect Repellent For Use On Kids	Solution	5.0%
24654	Domestic	S. C. Johnson And Son, Limited	OFF! Insect Repellent 3 - Unscented	Pressurized Product	7.0%
24656	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Lotion Insect Repellent For Use On Kids	Emulsifiable Concentrate or Emulsion	7.5%
24662	Domestic	9272-9771 Quebec Inc.	Ungava Insect Repellent 30% Deet Cream	Emulsifiable Concentrate or Emulsion	30.0%
24723	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods 3 Insect Repellent	Pressurized Product	25.0%
24975	Domestic	Daki Ltee	Bug-Z-Away Gel	Solution	10.0%
25368	Domestic	Daki Ltee	Bug-Z-Away Spray	Solution	10.0%
25543	Domestic	Chasse-moustique Buzz-Up	Buzz-Up Insect Repellent For Use On Kids	Solution	7.5%
25567	Domestic	Daki Ltee	Bug-Z-Away Intense Spray	Solution	29.4%
26424	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Magicolour Disappearing Purple Insect Repellent 1	Emulsifiable Concentrate or Emulsion	7.1%
26540	Domestic	Plz Corp.	K-G Insect Repellent IX	Pressurized Product	30.0%
26541	Domestic	Plz Corp.	K-G Insect Repellent X	Pressurized Product	15.0%
26542	Domestic	Plz Corp.	K-G Insect Repellent XI	Pressurized Product	25.0%
26543	Domestic	Plz Corp.	K-G Insect Repellent VIII	Pressurized Product	10.0%
26642	Domestic	Canadian Tire Corp. Ltd.	Muskol Insect Repellent Aerosol	Pressurized Product	23.5%
26912	Domestic	Canadian Tire Corp. Ltd.	Muskol Insect Repellent Pump Spray	Solution	30.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
27072	Domestic	The Great Woods, Llc.	Great Outdoors Insect Repellent Pressurized Spray	Pressurized Product	25.0%
27097	Domestic	S. C. Johnson And Son, Limited	OFF! Insect Repellent Foam	Pressurized Product	10.0%
27112	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods Pump Spray Insect Repellent 4	Solution	25.0%
27162	Domestic	753146 Alberta Ltd. O/A Ultrasol Industries	Odorless Foam Tick & Mosquito Repellent	Pressurized Product	10.0%
27205	Domestic	Chasse-moustique Buzz-Up	Buzz-Up Lotion Insect Repellent	Emulsifiable Concentrate or Emulsion	30.0%
27234	Domestic	S. C. Johnson And Son, Limited	Deep Woods OFF! 6 Insect Repellent	Pressurized Product	20.0%
27244	Domestic	Lloyds Laboratories Inc.	Lloyds Insect Repellent Pressurized Spray II	Pressurized Product	25.0%
27254	Domestic	Croc Bloc Products Inc.	Croc Bloc Insect Repellent II Towelettes	Impregnated Fabric	30.0%
27324	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Spray Insect Repellent Family - Summer Splash	Solution	7.0%
27325	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Spray Insect Repellent For Use On Kids - Tropical Fresh	Solution	5.0%
27355	Domestic	Croc Bloc Products Inc.	Croc Bloc Insect Repellent Heavy Duty	Pressurized Product	30.0%
27406	Domestic	Tender Corporation	Ben's 30 Wilderness Formula	Solution	30.0%
27474	Domestic	S. C. Johnson And Son, Limited	OFF! Active Insect Repellent	Pressurized Product	15.0%
27534	Domestic	9272-9771 Quebec Inc.	Ungava Cream 7% Deet For Kids	Emulsifiable Concentrate or Emulsion	7.0%
27552	Domestic	Plz Corp.	K-G Insect Repellent Pump Spray 30%	Solution	30.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
27606	Domestic	Plz Corp.	K-G Insect Repellent Pump Spray 7.5%	Solution	7.5%
27613	Domestic	Croc Bloc Products Inc.	Croc Bloc Insect Repellent Pump Spray Lite	Solution	9.8%
27614	Domestic	Tender Corporation	Ben's® 30 Wipes	Solution	30.0%
27642	Domestic	World Famous Sales Of Canada Inc.	World Famous Deet-X Insect Repellent	Pressurized Product	30.0%
27646	Domestic	Les produits de Contrôle supérieur Inc/Superior Control Products Inc*	K-O Insect Repellent	Pressurized Product	30.0%
27671	Domestic	Dentec Safety Specialists Inc.	Skeetsafe Insect Repellent Towelettes - Adult	Impregnated Fabric	25.0%
27672	Domestic	Dentec Safety Specialists Inc.	Insect Repellent Towelettes - Children	Impregnated Fabric	10.0%
27677	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Aerosol Insect Repellent Tropical Fresh	Pressurized Product	7.0%
27792	Domestic	Aurorium LLC	Deet Insect Repellent 10	Emulsifiable Concentrate or Emulsion	10.0%
27793	Domestic	Aurorium LLC	Deet Insect Repellent 30	Emulsifiable Concentrate or Emulsion	30.0%
27895	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods Insect Repellent Towelettes	Impregnated Fabric	25.0%
27938	Domestic	Shoppers Drug Mart/ Pharmaprix	Life Brand Insect Repellent Pressurized Spray	Pressurized Product	15.0%
27939	Domestic	Shoppers Drug Mart/ Pharmaprix	Life Brand Insect Repellent Aloe Vera Pump Summer Fresh	Solution	7.5%
27955	Domestic	9272-9771 Quebec Inc.	Ungava 30% Deet Pump Spray	Solution	30.0%
27979	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Spray Insect Repellent 2 For Use On Kids	Solution	5.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
27980	Domestic	S. C. Johnson And Son, Limited	OFF! Skintastic Spray Insect Repellent 2	Solution	7.0%
28058	Domestic	S. C. Johnson And Son, Limited	OFF! Active Pump Spray Insect Repellent	Solution	25.0%
28088	Domestic	S. C. Johnson And Son, Limited	OFF! Active Lotion Insect Repellent	Emulsifiable Concentrate or Emulsion	7.5%
28182	Domestic	Shoppers Drug Mart/ Pharmaprix	Life Brand Insect Repellent Spray For Kids Fresh Scent	Solution	5.0%
28188	Domestic	Croc Bloc Products Inc.	Croc Bloc Insect Repellent Pump Spray	Solution	30.0%
28246	Domestic	Wal-Mart Canada Inc.	Great Value Insect Repellent	Pressurized Product	25.0%
28254	Domestic	Wal-Mart Canada Inc.	Great Value Insect Repellent Summer Fresh With Aloe Vera 7.5% Deet	Solution	7.5%
28288	Domestic	Les produits de Contrôle supérieur Inc /Superior Control Products Inc*	Superieur Insect Repellent Pump Spray 30%	Solution	30.0%
28340	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods Pump Spray Insect Repellent For Sportsmen	Solution	25.0%
28488	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Insect Repellent Towelettes	Impregnated Fabric	7.0%
28489	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Insect Repellent Towelettes 2	Impregnated Fabric	7.0%
28498	Domestic	Kuus Inc.	Mosquito Shield Kids & Family Three Hour Insect Repellent	Pressurized Product	10.0%
28547	Domestic	Tender Corporation	Ben's 30 Wilderness Formula Eco-Spray	Solution	30.0%
28561	Domestic	Wal-Mart Canada Inc.	Great Value Fresh Scent Insect Repellent For Kids	Solution	5.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
28564	Domestic	9272-9771 Quebec Inc.	Ungava No Fragrance	Emulsifiable Concentrate or Emulsion	30.0%
28565	Domestic	9272-9771 Quebec Inc.	Mosquito Screen Insect Repellent Pump Spray	Solution	30.0%
28581	Domestic	Plz Corp.	K-G Insect Repellent Pump Spray 5%	Solution	5.0%
28582	Domestic	Plz Corp.	K-G Insect Repellent Pump Spray 10%	Solution	10.0%
28636	Domestic	Kuus Inc.	Mosquito Shield Family Formula Insect Repellent Pump Spray 7.5	Solution	7.5%
28648	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Insect Repellent Smooth & Dry	Pressurized Product	15.0%
28649	Domestic	9272-9771 Quebec Inc.	Mosquito Screen Insect Repellent For Kids Cream 7% Deet	Emulsifiable Concentrate or Emulsion	7.0%
28692	Domestic	Daki Ltee	Bug-Z-Away Intense Gel	Solution	30.0%
28800	Domestic	9272-9771 Quebec Inc.	Ungava Insect Repellent	Pressurized Product	25.0%
28843	Domestic	Kuus Inc.	Mosquito Shield Active Formula Insect Repellent Pressurized Spray	Pressurized Product	15.0%
28844	Domestic	Kuus Inc.	Mosquito Shield Kids Formula Insect Repellent Pump Spray	Solution	5.0%
28846	Domestic	Kuus Inc.	Mosquito Shield Active Formula Insect Repellent Pump Spray	Solution	15.0%
28869	Domestic	Dentec Safety Specialists Inc.	Skeetsafe Insect Repellent 30 Pump Spray - Adult	Solution	30.0%
28870	Domestic	Dentec Safety Specialists Inc.	Skeetsafe Insect Repellent 10 Pump Spray-Child	Solution	10.0%
28871	Domestic	Dentec Safety Specialists Inc.	Skeetsafe Insect Repellent 25 Pressurized Spray-Adult	Pressurized Product	25.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
28897	Domestic	Shoppers Drug Mart/ Pharmaprix	Life Brand Insect Repellent	Pressurized Product	25.0%
28901	Domestic	Tender Corporation	Ben's Family Eco-Spray	Pressurized Product	10.0%
28902	Domestic	Tender Corporation	Ben's Family Wipes	Impregnated Fabric	10.0%
28903	Domestic	Tender Corporation	Ben's Family Spray	Solution	10.0%
28904	Domestic	Tender Corporation	Ben's Family Lotion	Solution	10.0%
28906	Domestic	Tender Corporation	Ben's 30 Spray	Solution	30.0%
28988	Domestic	Kuus Inc.	Mosquito Shield Wilderness Formula Insect Repellent Pump Spray	Solution	30.0%
28989	Domestic	Kuus Inc.	Mosquito Shield Wilderness Formula Insect Repellent Pressurized Spray	Pressurized Product	30.1%
28990	Domestic	Kuus Inc.	Mosquito Shield Family Formula Insect Repellent Pump Spray	Solution	7.5%
28991	Domestic	Kuus Inc.	Mosquito Shield Northern Formula Insect Repellent Pressurized Spray	Pressurized Product	25.0%
29019	Domestic	753146 Alberta Ltd. O/A Ultrasol Industries	Doktor Doom Maximum Strength Mosquito, Tick & Pesky Fly Repellent 30% Deet	Pressurized Product	30.0%
29497	Domestic	Canadian Tire Corp. Ltd.	Muskol Insect Repellent Lotion	Emulsifiable Concentrate or Emulsion	30.0%
29514	Domestic	Wal-Mart Canada Inc.	Great Value Insect Repellent Pump Spray	Solution	30.0%
29646	Domestic	The Great Woods, LLC	Great Outdoors Insect Repellent Spray Kids	Solution	5.0%
29931	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods Spray Insect Repellent 5	Solution	25.0%
29932	Domestic	S. C. Johnson And Son,	OFF! Deep Woods Spray Insect Repellent	Solution	25.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
		Limited	For Sportsmen 2		
29933	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Spray Insect Repellent Family	Solution	7.0%
29934	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Spray Insect Repellent Family Unscented	Solution	7.0%
29970	Domestic	The Great Woods, LLC	The Great Outdoors Insect Repellent Spray1	Pressurized Product	30.0%
30097	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods Insect Repellent Dry	Pressurized Product	25.0%
30239	Domestic	Le Groupe Jean Coutu (Pjc) Inc.	Personnelle Insect Repellent Aloe Vera Pump	Solution	7.5%
30247	Domestic	Le Groupe Jean Coutu (Pjc) Inc.	Personnelle For Kids Insect Repellent Spray	Solution	5.0%
30308	Domestic	Novella Brands Inc.	Dermaguard Skin-Friendly Insect Repellent Woods	Pressurized Product	15.0%
30309	Domestic	Novella Brands Inc.	Dermaguard Skin-Friendly Insect Repellent Maximum Protection	Pressurized Product	30.0%
30310	Domestic	Novella Brands Inc.	Dermaguard Skin-Friendly Insect Repellent Family	Solution	10.0%
30311	Domestic	Novella Brands Inc.	Dermaguard Skin-Friendly Insect Repellent Sport	Solution	15.0%
30314	Domestic	Novella Brands Inc.	Dermaguard Skin-Friendly Insect Repellent For Kids	Solution	5.0%
30315	Domestic	Novella Brands Inc.	Dermaguard Skin-Friendly Insect Repellent Foam	Pressurized Product	10.0%
30555	Domestic	Federated Co-Operatives Limited	Co-Op Gold Insect Repellent (25% Deet)	Pressurized Product	25.0%
30576	Domestic	Business Helpers' Depot Inc.	Sure Guard 5% Deet Insect Repellent	Pressurized Product	5.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
30577	Domestic	Business Helpers' Depot Inc.	Sure Guard 15% Deet Insect Repellent	Pressurized Product	15.0%
30579	Domestic	Business Helpers' Depot Inc.	Sure Guard 30% Deet Insect Repellent	Pressurized Product	30.0%
30598	Domestic	S. C. Johnson And Son, Limited	OFF! Deep Woods For Sportsmen Insect Repellent Dry	Pressurized Product	25.0%
30751	Domestic	Kuus Inc.	Mosquito Shield Maximum Protection Combat Formula	Pressurized Product	30.0%
30807	Domestic	The Great Woods, LLC	Great Outdoors Insect Repellent Spray	Solution	7.5%
30808	Domestic	The Great Woods, LLC	Great Outdoors Insect Repellent Pressurized Spray	Pressurized Product	10.0%
30853	Domestic	Novella Brands Inc.	5% Dermaguard Skin Friendly Insect Repellent - Kids/Family Continuous Spray	Pressurized Product	5.0%
30859	Domestic	Novella Brands Inc.	15% Dermaguard Skin Friendly Insect Repellent - Woods/Sport Continuous Spray	Pressurized Product	15.0%
30860	Domestic	Novella Brands Inc.	30% Dermaguard Skin Friendly Insect Repellent - Maximum Protection Continuous Spray	Pressurized Product	30.0%
30992	Domestic	Kuus Inc.	Mosquito Shield Wilderness Formula Insect Repellent Lotion	Emulsifiable Concentrate or Emulsion	30.0%
30997	Domestic	Novella Brands Inc.	Dermaguard Skin-Friendly Insect Repellent Maximum Protection/Woods	Solution	30.0%
31084	Domestic	S. C. Johnson And Son, Limited	OFF! Explore Insect Repellent 3	Pressurized Product	25.0%
31085	Domestic	S. C. Johnson And Son, Limited	OFF! Explore Insect Repellent 1	Pressurized Product	25.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
31147	Domestic	Novella Brands Inc.	Kombat Insect Repellent For Kids	Solution	5.0%
31148	Domestic	Novella Brands Inc.	Kombat Insect Repellent 30% Deet Maximum Defence	Pressurized Product	30.0%
31150	Domestic	Novella Brands Inc.	Kombat Insect Repellent 5 % Deet Family	Pressurized Product	5.0%
31151	Domestic	Novella Brands Inc.	Kombat Insect Repellent 15% Deet Active Sport	Pressurized Product	15.0%
31152	Domestic	Novella Brands Inc.	Kombat Insect Repellent Sport	Solution	15.0%
31155	Domestic	Novella Brands Inc.	Kombat Insect Repellent Family	Solution	10.0%
31241	Domestic	Quality Home Products	Quality Home Products Insect Repellent 25% Pump Spray	Solution	25.0%
31290	Domestic	Les Marques Metro S.E.N.C.	Selection For Kids Insect Repellent Spray	Solution	5.0%
31291	Domestic	Les Marques Metro S.E.N.C.	Selection Insect Repellent Spray	Solution	5.0%
31384	Domestic	Wal-Mart Canada Inc.	Great Value Insect Repellent 25% Deet	Solution	25.0%
31385	Domestic	Shoppers Drug Mart/Pharmaprix	Life Brand Insect Repellent 25% Pump Spray	Solution	25.0%
31423	Domestic	Kuus Inc.	Mosquito Shield Wilderness Formula 1 Insect Repellent	Solution	30.0%
31438	Domestic	Novella Brands Inc.	Kombat Personal Insect Repellent - 15% Deet - For Gardeners	Pressurized Product	15.0%
31548	Domestic	9272-9771 Quebec Inc.	Ungava Insect Repellent Pump Spray-Children	Solution	7.5%
31575	Domestic	Federated Co-Operatives Limited	Co-Op Gold Insect Repellent Spray For Kids	Solution	5.0%
31601	Domestic	Kuus Inc.	Mosquito Shield Combat Formula I Insect Repellent	Solution	30.0%
31762	Domestic	Business Helpers' Depot Inc.	Sureguard Personal 2 Hrs Insect Repellent	Pressurized Product	5.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
31765	Domestic	Business Helpers' Depot Inc.	Sureguard Personal 3 Hrs Insect Repellent	Pressurized Product	7.0%
31767	Domestic	Business Helpers' Depot Inc.	Sureguard Personal 4 Hrs Insect Repellent	Pressurized Product	11.0%
31775	Domestic	Business Helpers' Depot Inc.	Sureguard Personal 5 Hrs Insect Repellent	Pressurized Product	15.0%
31778	Domestic	Business Helpers' Depot Inc.	Sureguard Personal 6 Hrs Insect Repellent	Pressurized Product	22.0%
31818	Domestic	Business Helpers' Depot Inc.	Sureguard 4hr Insect Repellent Pump Spray	Solution	11.0%
31819	Domestic	Business Helpers' Depot Inc.	Sureguard 6hr Insect Repellent Pump Spray	Solution	22.0%
32156	Domestic	Primmed B.V.	Care Plus Deet 30% Insect Repellent Pump Spray	Solution	30.0%
32323	Domestic	Intec Pharmacal Inc.	Coleman 7.5% Deet Insect Repellent Pump	Solution	7.5%
32324	Domestic	Intec Pharmacal Inc.	Coleman 10% Deet Insect Repellent Aerosol	Pressurized Product	10.0%
32537	Domestic	Business Helpers' Depot Inc.	Sure Guard Insect Repellent - 22% Deet	Pressurized Product	22.0%
32538	Domestic	Business Helpers' Depot Inc.	Sure Guard Insect Repellent - 30% Deet	Pressurized Product	30.0%
32646	Domestic	Plz Corp.	K-G Insect Repellent Ix Max	Pressurized Product	30.0%
32647	Domestic	Plz Corp.	Insect Repellent Pump Spray 30%-Max	Solution	30.0%
32738	Domestic	Plz Corp.	K-G Insect Repellent X-Dry	Pressurized Product	15.0%
32745	Domestic	Intec Pharmacal Inc.	Coleman Insect Repellent Lotion	Emulsifiable Concentrate or Emulsion	30.0%
32776	Domestic	Intec Pharmacal Inc.	Coleman Insect Repellent 30% Deet Aerosol	Pressurized Product	30.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
32777	Domestic	Intec Pharmacal Inc.	Coleman Insect Repellent 30% Deet Pump	Solution	30.0%
32778	Domestic	Intec Pharmacal Inc.	Coleman Insect Repellent Dry Aerosol	Pressurized Product	15.0%
32779	Domestic	Wal-Mart Canada Inc.	Great Value Dry Spray Insect Repellent	Pressurized Product	15.0%
32791	Domestic	Chasse-moustique Buzz-Up	Buzz-Up Insect Repellent - 30% Deet	Pressurized Product	30.0%
32857	Domestic	Empack Spraytech Inc.	Emzone 30% Deet - Skin Friendly Insect Repellent - Maximum Protection Continuous Spray	Pressurized Product	30.0%
32859	Domestic	Empack Spraytech Inc.	Emzone 15% Deet - Skin-Friendly Insect Repellent - Continuous Spray	Pressurized Product	15.0%
32894	Domestic	Shoppers Drug Mart/Pharmaprix	Life Brand Sport Insect Repellent	Pressurized Product	30.0%
32940	Domestic	Empack Spraytech Inc.	Emzone 30% Deet Insect Repellent Lotion	Emulsifiable Concentrate or Emulsion	30.0%
32964	Domestic	Novella Brands Inc.	Kombat 30% Deet Insect Repellent Wipes	Impregnated Fabric	30.0%
32990	Domestic	Empack Spraytech Inc.	Emzone 30% Deet Insect Repellent Wipes	Impregnated Fabric	30.0%
33057	Domestic	Novella Brands Inc.	Kombat 30% Deet Mosquito Repellent Wipes	Impregnated Fabric	30.0%
33119	Domestic	Novella Brands Inc.	Kombat 30% Deet Insect Repellent Lotion	Emulsifiable Concentrate or Emulsion	30.0%
33485	Domestic	753146 Alberta Ltd. O/A Ultrasol Industries	Doktor Doom Premium 30% Deet Tick & Mosquito Repellent Wipes	Impregnated Fabric	30.0%
33587	Domestic	Wal-Mart Canada Inc.	Great Value Tick Repellent	Pressurized Product	25.0%
33598	Domestic	Quality Home Products	QHP Insect Repellent	Pressurized Product	25.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
33618	Domestic	Canadian Tire Corp. Ltd.	Muskol Backcountry Repellent 30% Deet	No_Data	30.0%
33750	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Spray Insect Repellent Family - Clean Feel	Solution	7.0%
33752	Domestic	S. C. Johnson And Son, Limited	OFF! FamilyCare Spray Insect Repellent For Use On Kids - Floral Fresh	Solution	5.0%
33873	Domestic	Canadian Tire Corp. Ltd.	Muskol Backcountry Tick Repellent	Solution	30.0%
33874	Domestic	Canadian Tire Corp. Ltd.	Muskol Family & Kids Iii Insect Repellent	Pressurized Product	10.0%
33875	Domestic	Canadian Tire Corp. Ltd.	Muskol Family & Kids II Insect Repellent	Solution	10.0%
33876	Domestic	Canadian Tire Corp. Ltd.	Muskol Insect Repellent VIII	Solution	25.0%
34020	Domestic	Intec Pharmacal Inc.	Bug Out! 30% Deet Aerosol	Pressurized Product	30.0%
34046	Domestic	Intec Pharmacal Inc.	Bug Out! 30% Deet Lotion	No_Data	
34393	Domestic	Canadian Shield Insect Repellent Inc	Canadian Shield Insect Repellent Aerosol	Pressurized Product	30.0%
34395	Domestic	Canadian Shield Insect Repellent Inc	Canadian Shield Insect Repellent Pump Spray	Solution	30.0%
34496	Domestic	The Great Woods, LLC	Great Outdoors Dry Deet Spray	Pressurized Product	15.0%
34630	Domestic	Canadian Shield Insect Repellent Inc	Canadian Shield Tick Repellent	Pressurized Product	30.0%
34697	Domestic	Kuus Inc.	Savvy Insect Repellent 30% Deet	No_Data	30.1%
34725	Domestic	753146 Alberta Ltd. O/A Ultrasol Industries	Doktor Doom Tick Repellent For Clothing + (Plus)	Pressurized Product	30.0%
34917	Domestic	Le Groupe Jean Coutu (Pjc) Inc.	Personnelle Insect Repellent1	Pressurized Product	25.0%
35288	Domestic	Canadian Tire Corp. Ltd.	Muskol Active Insect Repellent	No_Data	15.0%
35291	Domestic	Canadian Tire Corp. Ltd.	Muskol Family & Kids Insect Repellent Iv	No_Data	15.0%

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
35371	Domestic	Aerokure International Inc.	Ungava Insect Repellent	Pressurized Product	25.0%
35372	Domestic	Aerokure International Inc.	Ungava 30% Deet Pump Spray	Solution	30.0%
35386	Domestic	Dentec Safety Specialists Inc.	Skeetsafe Insect Repellent 25% Pressurized Spray	Pressurized Product	25.0%
35388	Domestic	Dentec Safety Specialists Inc.	Skeetsafe Insect Repellent 30% Pump Spray	Solution	30.0%

[1] as of 23 July 2025, excluding discontinued products or products with a submission for discontinuation

Appendix II Registered uses of DEET in Canada

Table 1 Registered domestic uses of DEET (DTU) in Canada[1, 2]

Site	Pests	Formulations	Application method and equipment	Maximum single application rate (g a.i./ha)	Maximum cumulative application rate per year	Maximum number of applications per day	Minimum interval between applications (hours)
Use-Site Category 26 – Human Skin, Clothing and Proximal Sites							
Human skin (12 years of age or older)	Repels: black flies, biting midges, chiggers, deer flies, stable flies, mosquitoes, ticks	Impregnated fabric, solution, emulsifiable concentrate, pressurized product	Towelette, spray pump, applied by hand, pressurized spray	Not required	Not required	3–12	2–8
Human skin (2 to 12 years of age)	Repels: black flies, biting midges, chiggers, deer flies, stable flies, mosquitoes, ticks	Impregnated fabric, solution, emulsifiable concentrate, pressurized product	Towelette, spray pump, applied by hand, pressurized spray	Not required	Not required	5	2–8
Human skin (6 months to 2 years of age)	Repels: black flies, biting midges, chiggers, deer flies, stable flies, mosquitoes, ticks	Impregnated fabric, solution, emulsifiable concentrate, pressurized product	Towelette, spray pump, applied by hand, pressurized spray	Not required	Not required	1	24
Clothing (6 months to 2 years of age)	Repels: black flies, biting midges, chiggers, deer flies, stable flies, mosquitoes, ticks	Solution, pressurized product	Spray pump, pressurized spray	Not required	Not required	1	24

Site	Pests	Formulations	Application method and equipment	Maximum single application rate (g a.i./ha)	Maximum cumulative application rate per year	Maximum number of applications per day	Minimum interval between applications (hours)
Clothing (2 to 12 years of age)	Repels: black flies, biting midges, chiggers, deer flies, stable flies, mosquitoes, ticks	Solution, pressurized product	Spray pump, pressurized spray	Not required	Not required	5	2–8
Clothing (12 years of age or older)	Repels: black flies, biting midges, chiggers, deer flies, stable flies, mosquitoes, ticks	Impregnated fabric, solution, pressurized product	Towelette, spray pump, pressurized spray	Not required	Not required	3–12	2–8

[1] as of 24 February 2025 excluding discontinued products or products with a submission for discontinuation

[2] all information is derived from registered product labels

Appendix III Toxicology information for health risk assessment

Table 1 Toxicology reference values for use in the health risk assessment for DEET

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Dermal (short- to intermediate-term)	90-day dermal toxicity study in the rat	NOAEL = 300 mg/kg bw/day ↓bw, ↓food efficiency (♂); inflammation of the kidneys, hyaline casts (♀).	100
Acute incidental oral (children)	Acute neurotoxicity study in the rat (oral)	NOAEL = 50 mg/kg bw ↓reaction to pain, ↓vertical activity, ↑vocalization	100
Cancer	No treatment-related tumours were observed; therefore, a cancer risk assessment is not required.		

[1] Target MOE refers to a target margin of exposure for residential assessments

Table 2 Summary of toxicology studies for DEET

NOTE: Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to body weight) weight unless otherwise noted.

Note: Unless otherwise specified, studies listed in this table are considered Acceptable according to Information Note: Determining Study Acceptability for use in Pesticide Risk Assessments.

Study type/ Animal/PMRA No.	Study results
Toxicokinetic studies	
Toxicokinetic - ADME (gavage and dermal) Charles River rat PMRA No. 1126612	Mass balance – Single low-dose via oral or dermal route of ^{14}C-DEET (100 mg/kg bw; in petroleum ether) or single high oral dose (500 mg/kg bw; in petroleum ether), or repeated oral low-dose of unlabeled DEET for 13 days, followed by a labeled dose on day 14. Distribution at peak blood concentration experiment was performed with a single oral or dermal low-dose. **Absorption:** Peak blood concentrations were observed at 0.5 hr in ♂ and at 2 hrs in ♀ via oral dosing. No clear peak was observed following dermal dosing; rather, a plateau between 1 hr and 6 hrs was observed in both sexes. The peak blood level of radioactivity for rats administered ^{14}C-DEET by the dermal route was more than an order of magnitude lower than the levels observed in rats administered ^{14}C-DEET orally.

Study type/ Animal/PMRA No.	Study results
	Distribution: After 7 days PD, radioactivity was distributed in all tissues examined, regardless of the route of dosing or dosing regimen, and very little accumulated within the tissues (0.15% to 0.67% of the AD, mostly in the carcass). The liver, kidneys, lungs, spleen, and whole blood contained the highest radioactivity levels on a ppm basis. The concentrations in individual tissues were all below 1 ppm, except in the single oral high-dose group where peak concentrations of 2.9 ppm and 4.0 ppm were detected in whole blood samples of ♂ and ♀, respectively. Slightly higher tissue concentrations were noted in ♀. At 0.5/2 hrs (♂/♀) following single oral low dose or 3.5 hrs (♂/♀) following dermal dosing, the highest concentration of radioactivity at time of peak blood concentration occurred in the kidneys (~5-fold higher than blood plasma from oral dosing; ~8-fold higher than plasma in dermal dosing). **Excretion:** No sex differences were observed and the excretion profile was similar regardless of dosing regimen. Total recovery of radioactivity following various dosing regimens ranged from 88% to 94% of the AD. Rapid excretion was observed, predominantly in urine (87% when exposed to a single low or high oral dose in ♂s; a range of 85% to 89% when exposed to a single low or high oral dose in ♀s; 91% when exposed to a repeated oral low-dose in both sexes; 78/74% of AD dermally (♂/♀)) and minimally via feces (3.5% to 5.9%/3.1% to 4.9% (♂/♀) of AD orally; 4.0%/7.0% of AD (♂/♀) via dermal) after 7 days PD. The fastest rate of elimination was detected following repeated oral low-dose (82% to 85% excreted within 12 hrs). Following a single oral high-dose, 34% to 51% of the AD was eliminated by 12 hrs (slightly slower), and 71% to 77% of the AD eliminated by 24 hrs. The slowest rate of excretion was from a single dermal low-dose, with only 12% to 16% of the AD eliminated after 24 hrs. **Metabolism:** Two major metabolites were identified. An oxidized metabolite (methyl group to a carboxylic acid; DCBA) accounted for 46% to 59% of the AD in urine in all dosing regimens. An oxidized + dealkylated metabolite (EACB) accounted for 10% to 17% of the AD in urine; however, only ~ 3% AD was accounted for in ♂s exposed to a single low oral or dermal dose. Two other minor metabolites were detected but not identified as they each accounted for <10% of the AD. No unchanged DEET was detected in excreta.
Toxicokinetic – Expired air concentrations	Single dose of ^{14}C-DEET (in petroleum ether) at 100 mg/kg bw. Twenty-four hrs PD, 0.013% and 0.016% of total radioactivity was

Study type/ Animal/PMRA No.	Study results
(gavage and dermal) Charles River rat PMRA No. 1126611	recovered following a single oral dose, whereas 0.014% and 0.016% total radioactivity was recovered following a single dermal dose (♂/♀), respectively, via expired air.
Toxicokinetic – Plasma concentrations (gavage) Sprague-Dawley rat PMRA No. 1176459	Single dose of unlabeled DEET at 200 mg/kg bw (undiluted). DEET was observed in the blood 15 mins PD, plateaued within 45 mins (♂) and 15 mins (♀). However, the data for ♀ was more variable in the 2 hrs following dosing.
Toxicokinetic - Plasma concentrations (gavage) Sprague-Dawley rat PMRA No. 1190674	Single dose of unlabeled DEET at 200 mg/kg bw (undiluted). Mean peak DEET plasma concentrations were observed within 30 mins PD (7.1/15.2 µg/mL, ♂/♀). The elimination of DEET from plasma after reaching peak concentration was biphasic. DEET was rapidly absorbed from the stomach, distributed in the body within 2 to 4 hrs PD, and eliminated from plasma within 12 hrs. The mean DEET plasma concentration was greater for ♀ than ♂. The mean AUC was 22.9/79.2 µg hrs/mL (♂/♀).
Toxicokinetic – Plasma concentrations (dermal) Sprague-Dawley rat PMRA No. 1176460	Single dose of unlabeled DEET at 1000 mg/kg bw (undiluted) or repeated dosing of unlabeled DEET at 1000 mg/kg bw/day (undiluted) for 5 consecutive days. ♂: Blood plasma concentrations plateaued from 2 to 12 hrs PD following both single or repeated exposures. The average DEET plasma concentrations were 4.6 and 4.4 µg/mL following single and repeated dosing, respectively, during this period. The mean AUC was 90 and 101 µg hrs/mL for single and repeated administration, respectively. The half-life of plasma elimination values were 6.9 hrs and 8.7 hrs for single and repeated administration, respectively. ♀: Blood plasma concentration following a single application did not plateau until 4 hrs PD. No plateau was detected with repeated dosing but peak concentrations were achieved 8 hrs PD, and then ↓ substantially by 12 hrs PD. The level of DEET was > than in ♂ for the first 8 hrs and 12 hrs following repeated exposure and single exposure, respectively. The average DEET plasma concentration was 24 µg/mL (4-12 hrs) after a single dose and 17 µg/mL (8 hrs) following repeated administration. The mean AUC was 368 and 135 µg hrs/mL, and the half-life of elimination of DEET from plasma was 2.2 and 2.9 hrs from single and repeated-dosing, respectively.

Study type/ Animal/PMRA No.	Study results
Toxicokinetic – Plasma concentrations (capsule) Beagle dog PMRA No. 1176461	Repeated dosing of unlabeled DEET for 4 consecutive days at 75 mg/kg bw/day in white mineral oil. Mean maximum DEET plasma concentration was 18 µg/mL after the first dose and 14 µg/mL after the final dose (♂) and 14 and 13 µg/mL after the first and final doses, respectively (♀). DEET was absorbed rapidly from the gastrointestinal tract with maximum DEET plasma concentrations occurring within 10 to 60 mins. The mean plasma elimination half-life was 28 mins, indicating rapid elimination. DEET plasma concentrations were below the LOQ within 6 hrs PD. No evidence of accumulation of DEET in plasma.
Half-life determination (intravenous injection) – non guideline Beagle dog PMRA No. 2934207	**Acceptable with limitations** Single dose of unlabeled DEET at 10 mg/kg bw (undiluted) Maximum plasma concentration detected 5 mins after injection. $AUC_{0\text{-}inf}$ = 32085 ng hr/mL. Half-life = 0.75 hrs. Mean apparent volume of distribution = 27 L. **Limitations:** Small group size (1/sex)
Toxicokinetic – Absorption, metabolism, and excretion (dermal) Human PMRA No. 2246887	Single dose of ^{14}C-DEET undiluted or as a 15% solution in ethanol on the forearm for 8 hrs. **Absorption:** Radioactivity was detected in the plasma beginning at 2 hrs PD, and peaked at 6 hrs and 4 hrs in the undiluted and 15% solution groups, respectively. Plasma radioactivity was below LOQ by 16 hrs PD in both groups. It was estimated that mean values of 5.6% and 8.4% of the AD were absorbed through skin and recovered in excreta for the undiluted and 15% solution groups, respectively. **Excretion:** Rapid, predominantly in urine and minimally in feces. **Metabolism:** Six metabolites identified; two major urinary metabolites were characterized: oxidation of the aromatic methyl group to a carboxylic acid (DCBA) and oxidation of aromatic methyl group to carboxylic acid group + dealkylation of the amide group (EACB). No unchanged DEET was detected in urine.
Toxicokinetic – Plasma concentrations (dermal) Human PMRA No. 1176463	Repeated dosing of unlabeled DEET (111–154 mg/kg bw/day, undiluted, in ♂s and 91–143 mg/kg bw/day in ♀s) for 8 hrs/day for four days. DEET was first quantifiable in blood 3–4 hrs (♀) or 0.5–3 hrs (♂) following application on days 1 and 4. DEET plasma concentrations ↑ during the exposure period. After 1 day

Study type/ Animal/PMRA No.	Study results
	of exposure, DEET plasma levels were generally ↓ to near or below the lower LOQ. Maximum DEET plasma levels tended to ↓ with repeated applications. Mean maximum DEET plasma concentrations ranged between 254 ng/mL and 430 ng/mL (♀) and between 487 ng/mL and 618 ng/mL (♂). The elimination half-life of DEET was 6.3/7.2 hrs (♂/♀).
Toxicokinetic - Whole Body Autoradiography (Mouse) and Urinary Excretion (Human) (dermal) Mouse, human PMRA No. 3248577	Mouse (whole body autoradiography): single dose of ^{14}C-DEET (15 mg/kg bw in 0.3% ethanol); washed after 2 hrs; sacrificed after 2 hrs, 6 or 36 days PD. Mouse (urinary ^{14}C excretion): single dose of ^{14}C-DEET (15 mg/kg bw in 0.3% ethanol) while under anesthetization, and urine was collected 2 hrs PD. Human: single dose of ^{14}C-DEET (0.12 mg/kg bw in 25% solution of absolute ethanol) on the forearm, and urine was collected 2 days PD. **Distribution in mice (whole body autoradiography):** Two hrs PD, highest tissue concentrations of radioactivity were detected in the lacrimal gland, liver, kidney and nasal mucosa. There were also higher concentrations in the bile and in parts of the intestinal contents as well as in the urine, indicating biliary and urinary excretion. Six days PD, radioactivity was only observed on the applied skin and in the urinary bladder, and 36 days PD, it was only detected on the application site. **Urinary excretion in mice:** 13% was excreted during the first 2.5 hrs, and about 34% during the first 2 days. When washing the application area, an average of 6% of the applied radioactivity was recovered. **Urinary excretion in humans:** 5.5% and 3.8% of AD was recovered from the urine 48 hrs PD from the first and second trials of the experiments, respectively. When washing the application area 8 hrs PD, 8% and 15% were recovered from the first and second trials, respectively.
In vitro Comparative Metabolism Rat, Mouse and Human Liver Microsomes, and Human P450 Isoforms PMRA No. 3607612	**Acceptable with limitations.** Human, rat and mouse liver microsomes had ↑affinity and ↑intrinsic clearance for ring hydroxylation (DHMB formation) than for ET formation. Human liver microsomes exhibited higher K_M values (lower affinity) than those from rats or mice, and exhibited ↓intrinsic clearance rate for both metabolites compared to rats. The mouse liver microsomes CL_{int} was similar to that of human liver microsomes. When liver

Study type/ Animal/PMRA No.	Study results
	microsomes from mice were treated with the highest concentration, there was a significant ↑V_{max} and intrinsic clearance of DHMB[13] and ET, indicating that DEET induced its own metabolism. Among 15 different human P450 isoforms screened, only CYP1A2, CYP2B6, CYP2D6*1 and CYP2E1 displayed detectable DHMB metabolite production. Production of DHMB metabolite was generally much higher than that of the ET metabolite. Isoforms producing detectable amounts of ET metabolite included CYP3A4, CYP3A5, CYP2A6, and CYP2C19. These isoforms produced no detectable amounts of the DHMB metabolite. Overall, the study concluded that DEET was more efficiently metabolized by rat microsomes than human or mouse microsomes. **Limitations:** Individual data was not provided and the test substance was not adequately characterized; however, it was indicated that the test substance was commercially obtained.
In vitro Metabolism – Non-guideline Human Plasma and Liver Microsomal Enzymes PMRA No. 3607624	**Acceptable with limitations.** Following incubation with human plasma for 8 hrs, DEET average percentage recovery was 78% indicating that DEET was not efficiently metabolized by human plasma esterases in vitro. Following incubation with human liver microsomal preparations with an NADPH-generating system, DEET was efficiently metabolized. m-Toluamide was identified as a metabolite of DEET in human liver microsomal incubates, with K_M and V_{max} values of 62 mM and 112 pmol min^{-1} mg^{-1} of protein, respectively. This finding indicated that DEET was metabolized through oxidative N,N-deethylation in human liver microsome preparations. The study indicated that DEET is mainly metabolized by liver cytochrome oxidase enzymes. **Limitations:** Raw data not provided and most of the results were presented graphically only.
In Vitro Metabolism – Non-guideline Wistar Rat Liver Microsomes	**Acceptable with limitations.** The half-life of DEET was 10 and 15 mins (♂/♀). At 2 hrs after incubation, 58% and 16% of DEET was metabolized (♂/♀). The rate of accumulation of DHMB and ET metabolites were different in liver

[13] Referred to in the published study report as BALC.

Study type/ Animal/PMRA No.	Study results
PMRA No. 3607639	microsomes between ♂ and ♀. Microsomes from ♂s metabolized DEET much faster relative to ♀s. The rate of metabolism leveled off at 90 mins in both sexes. **Limitations:** Individual data was not provided by the study author, and the test substance was not adequately characterized.
Acute toxicity studies	
Acute Oral Toxicity (gavage) Sprague-Dawley rat PMRA No. 1466105	LD_{50} = 1944/1000 to 2000 mg/kg bw (♂/♀). Clinical signs included hunched or prone posture and hypoactivity. **Slight acute toxicity.**
Acute Oral Toxicity (gavage) Sprague-Dawley rat PMRA No. 2934211	LD_{50} = 3400/1900 mg/kg bw (♂/♀). Clinical signs included hypoactivity, piloerection, irregular breathing, and hunched/prone posture; recovered by Day 3. **Slight acute toxicity.**
Acute Oral Toxicity (gavage) – Non-guideline Non-Guideline Wistar rat PMRA No. 3607611	**Acceptable with limitations.** Reported LD_{50} = 1130 mg/kg bw (♂) ↑cholesterol, ↓total protein, ↑AST, ↑ALP, ↓rel spleen wt **Limitations:** The study author indicated that the test substance was synthesized, and characterized spectroscopically; however, results of this analysis were not provided. Additionally, the number of animals tested (N = 4 ♂s) is less than required for guideline studies. The study authors appear to have dosed animals with 6400 mg/kg bw, and ↓ the dose until "max survival" was observed. The mortality data was not provided. In spite of this, the obtained LD_{50} indicated that DEET was of slight acute oral toxicity, which is consistent with the results obtained in guideline rat acute oral toxicity studies.
Acute Dermal Toxicity Sprague-Dawley rat PMRA No. 1466103	LD_{50} > 5000 mg/kg bw (♂/♀). **Low acute toxicity.**
Acute Dermal Toxicity Sprague-Dawley rat	LD_{50} > 5000 mg/kg bw (♂/♀). One female exhibited hypoactivity on day of application, but recovered after the first day.

Study type/ Animal/PMRA No.	Study results
PMRA No. 2934212	**Low acute toxicity.**
Acute Dermal Toxicity Sprague-Dawley rat PMRA No. 1413431	LD_{50} > 5000 mg/kg bw (♂/♀). **Low acute toxicity.**
Acute Dermal Toxicity Non-Guideline Swiss albino rat PMRA No. 3607611	**Acceptable with limitations.** Reported LD_{50} = 4525 mg/kg bw (♂). ↓PLT, ↓cholesterol, ↑glucose, ↓rel lung wt, ↑rel liver wt, ↑rel spleen wt. **Limitations:** The study author indicated that the test substance was synthesized, and characterized spectroscopically; however, results of this analysis were not provided. Additionally, the number of animals tested (N = 4 ♂s) is less than required for guideline studies. In spite of this, the obtained LD_{50} indicated that DEET was of low acute dermal toxicity, similarly to the results obtained in guideline rat acute dermal toxicity studies**.**
Acute Inhalation Toxicity (whole-body) Sprague-Dawley Rat PMRA No. 1139202	LC_{50} > 4.1 mg/L (♂/♀). Clinical signs included tremors, hypoactivity, and incoordination. **Low acute toxicity.**
Acute Inhalation Toxicity (whole-body) Sprague-Dawley rat PMRA No. 2934213	LC_{50} > 2.15 mg/L (♂/♀). Clinical signs included ocular and nasal discharge, irregular respiration, hunched posture, and hypoactivity during exposure; recovered by day 3. **Low acute toxicity.**
Eye Irritation New Zealand White rabbit PMRA No. 2934214	MAS = 25.44. MIS = 30.67 (24 hrs). Signs of irritation reversible by day 14. **Moderately irritating.**

Study type/ Animal/PMRA No.	Study results
Eye Irritation New Zealand White rabbit PMRA No. 2934203	MAS = 25.56. MIS = 32 (24 hrs). Signs of irritation reversible by day 7. **Moderately irritating.**
Dermal Irritation New Zealand White rabbit PMRA No. 1467112	MAS = 0.17 on the left side, 0.33 on the right side. MIS = 0.17 on the left side, 0.33 on the right side (28 hrs-4 days). Signs of irritation reversible by day 7. **Minimally irritating.**
Dermal Irritation New Zealand White rabbit PMRA No. 2934215	MAS = 0.778. MIS = 2.667 (1 hr). Signs of irritation reversible by 72 hrs. **Slightly irritating.**
Dermal Sensitization (Buehler method) Hartley guinea pig PMRA No. 2934216	Negative.
Dermal sensitization (Buehler method) Hartley guinea pig PMRA No. 2934205	Negative.
Short-term toxicity studies	
14-Day Oral Toxicity (diet) – Range-Finding Study Golden Syrian hamster PMRA No. 1237518	**Acceptable with limitations** **701/664 mg/kg bw/day:** bw loss wk 1, ↓overall bwg (♂/♀); ↓terminal bw (♂). **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
90-Day Oral Toxicity (diet)	NOAEL = 61 mg/kg bw/day (♂/♀). **≥ 304/305 mg/kg bw/day:** ↓bw (♂/♀); bw loss wk 1 (♂).

Study type/ Animal/PMRA No.	Study results
Golden Syrian hamster PMRA No. 1237501	**≥ 611/636 mg/kw bw/day:** ↓testes wt, small epididymides, small testes, cellular debris in lumen of epididymides, testicular tubular degeneration (♂); bw loss following the first week of dosing (♀). **3136/3131 mg/kg bw/day:** mortality, clinical signs of toxicity (only observed in animals that died before scheduled sacrifice: cold to touch, exposed skin area pale, one incidence of tremors in each sex), ↑K (♂/♀); moribund, ↓defecation, laboured breathing, ↑RBC, ↑HCT, ↓protein (♂); ↓ovary wt (♀).
90-Day Oral Toxicity (diet) CD-1 mouse PMRA No. 1237517	NOAEL = 1000 mg/kg bw/day (♂/♀). **≥ 1000 mg/kg bw/day:** ↑liver wt (♂/♀); hepatocellular hypertrophy (♀). (effects non-adverse at this dose) **3000 mg/kg bw/day:** ↓defecation, ↓bw, ↓bwg, ↓fc, ↓kidney wt, (♂/♀); hepatocellular hypertrophy (♂); hunched posture, ↓abs brain wt, single incidence of liver vacuolation (♀). **≥ 6000 mg/kg bw/day:** groups were eliminated on wk 3 due to mortality, clinical signs of toxicity such as tremors, hunched posture, laboured breathing, ↓ motor activity, moribund and eyes partially closed, as well as diet rejection.
90-Day Oral Toxicity (diet) Sprague-Dawley rat PMRA No. 1237502	NOAEL = 500/100 mg/kg bw/day (♂/♀). **≥ 100 mg/kg bw/day:** granular cast formation, multifocal chronic inflammation, positive hyaline droplet staining, and regenerative renal tubular epithelium in the kidneys (♂; kidney effects considered not relevant to human health risk assessment). **≥ 500 mg/kg bw/day:** ↓bw, ↓bwg, ↓fc, ↑BUN, ↑liver wt (♀). **≥ 1000 mg/kg bw/day:** bw loss wk 1, ↓bw, ↓bwg, ↓fc, ↓lymphocytes, epididymis inflammation (♂); ↓defecation, ↑K, ↓kidney wt (♀). **≥ 2000 mg/kg bw/day:** high carriage during locomotion, firm areas in abdomen (♂/♀); ↓defecation, bw loss (wks 1–2), ↓phosphorus, ↓abs brain wt, ↓kidney wt, liver necrosis (♂); mortality, laboured breathing, ↓activity, cool, pale, hunched posture, eyes partially closed, ↑RBC, ↑HCT, ↓MCV, ↓MCH, ↑K, ↑tot-bil, ↓protein, ↓albumin, ↓globulin, ↓glucose, ↓ovary wt, kidney regeneration (♀). **4000 mg/kg bw/day:** Group was eliminated after three wks of dosing due to mortality, signs of acute toxicity (hunched posture, and laboured breathing), and severe weight loss in wk 1, and diet rejection.

Study type/ Animal/PMRA No.	Study results
	Note: Due to severe body weight depressions, the study authors examined a full tissue complement from 10 randomly selected animals/sex from the control and 1000 mg/kg bw/day group, and a limited amount of tissues at 2000 mg/kg bw/day (liver, testis, kidney and all gross lesions only).
14-Day Oral Toxicity (diet) – Dose Range-Finding Study Beagle dog PMRA No. 1163662	**Acceptable with limitations** **≥ 90/56 mg/kg bw/day:** bw loss (♂/♀); ↓fc, ↓defecation in the first wk (♀). **15/43 mg/kg bw/day**: diarrhea, ↓defecation, single occurrence of red material in feces, ↓activity, thin appearance, diet rejection (leading to lower test substance intake in this group) (♂/♀); ↓fc (♂). **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
14-Day Oral Toxicity (capsule) – Dose Range-Finding Study Beagle dog PMRA No. 1163663	**Acceptable with limitations** **≥ 250 mg/kg bw/day:** frothy emesis, ptyalism (♂/♀); ↓activity, abnormal behaviour such as nodding or twitching of the head (♀). **500 mg/kg bw/day:** abnormal behaviour such as nodding or twitching of the head, prostration, ataxia, and convulsions (♂). **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
21-Day Oral Toxicity (diet) - non-guideline Beagle dog PMRA No. 1163665	**Acceptable with limitations** **99/88 mg/kg bw/day:** ↓defecation, emesis, thinness, dehydration (♂/♀); transient ↓bw, food rejection wk 1 (♂); discoloured feces and/or red material in feces, ↓bw and food rejection in one ♀ (♀). **Limitations:** Limited sample size and endpoints assessed, one dose tested, and no control group.
60-Day Oral Toxicity (diet) – Dose Range-Finding Study Beagle dog PMRA No. 1163666, 1163673	**Acceptable with limitations** **≥ 8.4/9.7 mg/kg bw/day:** diarrhea, emesis (♂/♀), ↑pituitary wt (♀). **29/30 mg/kg bw/day:** bw loss (♀). **93/92 mg/kg bw/day:** ↓ defecation (♂/♀), ↓adrenal wt (♀). **20/12 mg/kg bw/day**: ↓activity, thinness, bw loss first wk of dosing, ↓bw, ↓fc (diet rejection, leading to lower test substance intake in this group), ↓abs kidney wt, cytoplasmic vacuolization of tubules in the

Study type/ Animal/PMRA No.	Study results
	kidneys, hypocellularity of the bone marrow of the ribs, thymic atrophy (♂/♀); ↓liver wt, ↓spleen wt, thymic haemorrhage (♂); ↓body fat, ↓ovary wt (♀). **Note:** The dietary concentrations were altered in the high dose group as follows: 6000 ppm for wks 1–2, 4500 for wks 4–5, 3000 for wks 7–8; basal diets on wks 3 and 6 due to diet rejection. The mean test article consumption for the highest-dose tested group in the study (from weeks 0 to 8) was therefore 20/12 mg/kg bw/day. **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
60-Day Oral Toxicity (capsule) – Dose Range-Finding Study Beagle dog PMRA No. 2934217	**Acceptable with limitations** **≥ 125 mg/kg bw/day:** emesis, ptyalism, abnormal biting and scratching and head movements (♂/♀); convulsions, ↓fc (♂). **≥ 175 mg/kg bw/day:** ptosis (♂/♀); ataxia (♀). **225 mg/kg bw/day:** ataxia, ↓bw (♂); convulsion, ↓fc (♀). **Note:** Study terminated after 5 days due to acute toxicity; study authors concluded that the daily administration of DEET as a single bolus dose is not appropriate for longer-term studies. **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
60-Day Oral Toxicity (capsule, split dose) – Dose Range-Finding Study Beagle dog PMRA No. 1163661	**Acceptable with limitations** **≥ 50 mg/kg bw/day:** ptyalism (♂). **≥ 100 mg/kg bw/day:** ↓cholesterol (♂); ptyalism (♀). **400 mg/kw bw/day:** abnormal head movement, bw loss wk 1, ↓bwg, atrophy of the thymus (♂/♀); ↑thyroid wt, ↓testis/epididymis wt, lymphocytic infiltration of the kidneys (♂); trembling, ↓activity, ↓bw, ↓fc, ↓ adrenal wt, ↓heart wt, ↓kidney wt (♀). **Note:** The daily dose was divided into morning and afternoon doses administered after a one-hour feeding period to minimize the potential for acute effects and allow for higher doses of DEET to be tolerated. **Limitations:** Animals were previously dosed in a separate study; dose range-finding study with limited sample size and endpoints assessed.

Study type/ Animal/PMRA No.	Study results
12-Month Oral Toxicity (capsule, split dose) Beagle dog PMRA No. 1163660	NOAEL = 30 mg/kg bw/day (♂/♀). **≥ 100 mg/kg bw/day:** ↓defecation, ↓overall bwg, slight ↓cholesterol, brown pigment on mandibular lymph nodes (♂); tremors (beginning wk 32) (♀). **400 mg/kg bw/day:** ptyalism, bw loss on wk 1, ↓bw, ↓fc, ↓RBC, ↓HGB, ↓HCT, mononuclear cell infiltration in liver (♂/♀); abnormal head movements, ataxia, convulsions in one ♂, tremors, atrophy of the thymus (♂); ↑platelets, ↑thyroid/parathyroid wt, distended uterus with fluid, glandular hyperplasia of the uterus (♀). **Note:** The daily dose was divided into morning and afternoon doses administered after a one-hour feeding period to minimize the potential for acute effects and allow for higher doses of DEET to be tolerated.
90-Day Dermal Toxicity Sprague-Dawley rat PMRA No. 1237515	NOAEL (systemic) = 300 mg/kg bw/day (♂/♀) **≥ 100 mg/kg bw/day:** red areas at the application site, ↑incidence of acanthosis, diffuse/local scaling, abraded and scabbed skin (♂/♀); enlarged kidneys, granular casts, hyaline droplets in the tubular cells, regeneration of the tubules in the cortex, multifocal cortex inflammation of the kidneys (♂; kidney effects considered not relevant to human health risk assessment). **300 mg/kg bw/day:** ↑ liver wt (♀) (non-adverse). **1000 mg/kg bw/day:** ↓bwg, ↑kidney wt (♂/♀); ↓bw, ↓food efficiency, ↓glucose, ↑liver wt (♂); inflammation of the kidneys, hyaline casts (♀).
90-Day Dermal toxicity Micropig PMRA No. 1171189	NOAEL (systemic) = 1000 mg/kg bw/day (♂/♀). **≥ 100 mg/kg bw/day:** hyperkeratosis and desquamation at the application site (♂/♀); dry skin (mild), ↑testis wt (considered non-adverse since not associated with any microscopic histopathological findings) (♂) . **≥ 300 mg/kg bw/day:** acanthosis at the application site (♂/♀). **1000 mg/kg bw/day:** ↑liver wt, ↑kidney wt, ↑adrenal wt, (♂). All findings considered non-adverse since not associated with any microscopic histopathological findings.

Study type/ Animal/PMRA No.	Study results
Chronic Toxicity/Oncogenicity Studies	
18-Month Oncogenicity (diet) CD-1 mouse PMRA No. 1237510	NOAEL = 501/502 mg/kg bw/day (♂/♀). **501/502 mg/kg bw/day:** ↑liver wt (♂/♀) (non-adverse); ↑hyperplastic nodules of liver (equivocal) (♂). **1004/1005 mg/kg bw/day:** ↓bw, ↓fc, enlarged spleen, ↑lymphoid hyperplasia of spleen (♂/♀); ↓kidney wt, ↑bile duct hyperplasia, ↑incidence of mesenteric lymph node lymphoid hyperplasia, ↑incidence of inflammation of the mandibular salivary gland and urinary bladder (♂). **No evidence of tumourigenicity**
24-Month Chronic Oral Toxicity/Oncogenicity (diet) Sprague-Dawley rat PMRA No. 1163674	NOAEL = 101/100 mg/kg bw/day (♂/♀). **≥ 30/100 mg/kg bw/day:** ↑cholesterol (♀) (non-adverse). **101/402 mg/kg bw/day:** slight ↑ in mild hemorrhage of the pituitary gland (♂/♀); ↑testis wt (♂); ↓bw, ↓bwg, ↓fc, ↑liver wt, liver inflammation (♀). **No evidence of tumourigenicity.**
Developmental/Reproductive toxicity studies	
2-Generation Reproductive Toxicity (diet) Sprague-Dawley rat PMRA No. 1237504	**Acceptable with limitations** **Parental toxicity** NOAEL = 129/152 mg/kg bw/day (♂/♀). **≥ 32/38 mg/kg bw/day:** mottling inflammation of the kidneys, hyaline droplets, granular cast formation and tubular regeneration (F1 ♂; kidney effects considered not relevant to human health hazard assessment). **320/378 mg/kg bw/day:** ↓bw (F1♂ premating/P and F1♀ premating, gestation and lactation) (♂/♀); one mortality (P; dystocia), ↓bwg (F1 premating) (♂); ↑incidence of hair loss, ↓fc (F1) (♀). **Reproductive toxicity** NOAEL = 320/378 mg/kg bw/day (♂/♀). No adverse treatment-related effects on the reproductive parameters assessed. **Offspring toxicity**

Study type/ Animal/PMRA No.	Study results
	NOAEL = 152 mg/kg bw/day **152 mg/kg bw/day:** ↓bw (5%/6.8%) in F2 pups at PND 21 only (♂/♀). Note: The ↓bw at this dose level was limited to the weaning period where pups are exposed to the test substance through both milk and feed, likely resulting in an increased level of exposure. Given that offspring test substance intakes during this period were likely much higher than the external maternal doses used to establish the effect levels in this study, it was not considered appropriate to establish the offspring LOAEL based on the isolated decrease in pup body weight on PND 21 at this dose level. **378 mg/kg bw/day:** ↓bw in pups (F1: PND 4-21; F2: PND 7-21) (♂/♀). **No evidence of sensitivity of the young**. **Limitations:** The following parameters were not assessed: estrous cycle, sperm parameters, follicle counts, uterus, ovary, prostate, epididymides, seminal vesicle, brain, liver, kidney, spleen, pituitary, thyroid, and adrenal weights, histopathology of uterus with cervix in high dose and control animals, sexual maturation of offspring, functional observations (sensory function, reflex in pups and adults), physical landmarks in pups.
9-Week Dermal Toxicity - Effects on Spermatogenesis Non-Guideline Sprague-Dawley rat (♂) PMRA No. 1209941	NOAEL = 1000 mg/kg bw/day **1000 mg/kg bw/day:** ↑liver wt, ↑kidney wt. No treatment-related effects on sperm count, viability, morphology or testicular cytology.
Developmental toxicity (gavage) – Dose Range-Finding Study Sprague-Dawley rat PMRA No. 1237505	**Acceptable with limitations** **Maternal** **1000 mg/kg bw/day:** mortality, hypoactivity, ataxia, prostration, unkempt appearance, perioral wetness, urine stain, laboured breathing, ↓bw, ↓bwg, ↓fc, ulcerations of the glandular stomach, distended urinary bladder, one dam with sloughing of stomach lining and large, spongy, dilated kidneys with blood, another with gas-filled intestines, and liver discolouration. **Developmental**

Study type/ Animal/PMRA No.	Study results
	1000 mg/kg bw/day: ↓fetal bw. Only fetal bw and external malformations were assessed. **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
Developmental toxicity (gavage) Sprague-Dawley rat PMRA No. 1237506	**Acceptable with limitations** **Maternal** NOAEL = 250 mg kg/bw/day. **750 mg/kg bw/day:** mortality, hypoactivity, ataxia, ↓muscle tone, urine stains, ↑foot splay, perinasal encrustation, perioral wetness, twitching, prostration, unkempt appearance, ↓bwg, ↓fc, ↑liver wt, ulceration/sloughing of glandular stomach, distended urinary bladder in dams that died. **Developmental** NOAEL = 250 mg/kg bw/day **750 mg/kg bw/day:** ↓fetal bw. **No evidence of treatment-related malformations or sensitivity of the young.** **Limitations:** The maternal dosing period (GD 6-15) was shorter than required by the current test guideline (GD 6-20).
Developmental Toxicity (gavage) – Dose Range-Finding Study New Zealand White rabbit PMRA No. 1139193	**Acceptable with limitations** **Maternal** **≥ 250 mg/kg bw/day:** rapid respiration, ↓bwg (GD 6-9). **≥ 500 mg/kg bw/day:** mortality, ↓fc, sloughing and ulceration of the glandular stomach, gas-filled intestine, colour changes in lung and liver, reticular pattern on liver. **1000 mg/kg bw/day:** hypoactivity, ataxia, prostration, cold extremities, gasping, rapid or slow respiration, ↓bw, ↓bwg (GD 6-18), ↓liver wt, sloughing and ulceration of the non-glandular stomach. **Developmental** No developmental effects observed in the limited parameters assessed (fetal bw and external examinations only).

Study type/ Animal/PMRA No.	Study results
	Limitations: Dose range-finding study with limited sample size and endpoints assessed.
Developmental Toxicity (gavage) New Zealand White rabbit PMRA No. 1126607	**Acceptable with limitations** **Maternal** NOAEL = 100 mg/kg bw/day. **325 mg/kg bw/day:** slight bw loss (GD 6-9), ↓bwg (GD 6-18), ↓fc (GD 6-18). **Developmental** NOAEL = 100 mg/kg bw/day. **325 mg/kg bw/day:** delayed ossification of some interphalanges, ↑unilateral and bilateral rudimentary rib #13 on thoracic arch. **No evidence of treatment-related malformations or sensitivity of the young.** **Limitations:** The maternal dosing period (GD 6-18) was shorter than required by the current test guideline (GD 6-28).
Genotoxicity Studies	
Bacterial Reverse Mutation S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100) PMRA No. 1237507	Negative ± metabolic activation; tested up to cytotoxic concentrations.
Bacterial Reverse Mutation S. typhimurium (TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538) PMRA No. 3225533	**Acceptable with limitations** No treatment-related increases in mutation. **Limitations:** The test substance was not characterized; however, it was obtained from a commercial supplier. Unclear if the test was conducted up to cytotoxicity or solubility limit concentrations.
In vitro Mammalian Cell Gene Mutation (CHO-k1 cells)	**Acceptable with limitations** Negative ± metabolic activation; tested up to cytotoxic concentrations. **Limitation:** Purity of the test substance not specified.

Study type/ Animal/PMRA No.	Study results
PMRA No. 2934206	
In vitro Unscheduled DNA Synthesis Rat Primary Hepatocytes PMRA No. 1237509	Negative; tested up to cytotoxic concentrations.
In vitro Mammalian Chromosome Aberration Chinese Hamster Ovary (CHO) Cells PMRA No. 1237508	Negative ± metabolic activation; tested up to cytotoxic concentrations.
In vitro Mammalian Cell Comet Assay Non-Guideline Human nasal mucosa biopsies PMRA No. 3225204	**Acceptable with limitations** DEET showed a statistically significant dose-dependent ↓ in the % of undamaged cells. Authors reported no significant cytotoxic effects after incubation with DEET. Trypan blue positive cells ranged from 5% to 17% following DEET exposure. Trypan blue positive cells were not reported for the negative control. **Limitations:** The group size was not specified. The effect of metabolic activation was not assessed. The frequency/presence of hedgehog comets was not specifically discussed. There was no indication of the reason patients were undergoing nasal surgery that provided the opportunity for the study authors to obtain the biopsies, and therefore it was uncertain whether the biopsies were obtained from healthy nasal tissue.
Neurotoxicity studies	
Acute Neurotoxicity (gavage) Sprague-Dawley rat PMRA No. 1237530	**Acceptable with limitations** NOAEL = 50 mg/kg bw (♂/♀). **≥ 50 mg/kg bw:** mild salivation immediately PD (♂/♀) (not adverse). **≥ 200 mg/kg bw:** ↓vertical activity at 1 hr PD, ↑thermal response time at 1 hr PD (♂/♀); ↑vocalization (♂). **500 mg/kg bw:** ↑piloerection at 1 hr, 24 hrs PD, ↑thermal response time at 24 hrs PD, ↓horizontal activity, ↓time in movement at 1 hr PD

Study type/ Animal/PMRA No.	Study results
	(♂/♀); ↑ tremors at 24 hrs PD (♂). **Evidence of neurotoxicity** **Limitations:** No positive control data and high variability in the motor activity assessment.
2nd Generation + Neurotoxicity (dietary) Non-guideline Sprague-Dawley rat PMRA No. 1171190 (9-month maintenance period), 1237541 (neurotoxicity assessment period)	**Acceptable with limitations** NOAEL = not established (♂/♀). LOAEL = 38 mg/kg bw/day (♂/♀). This study used F2 animals from the 2-generation reproductive toxicity study (PMRA No. 1237504). Following weaning, all control and 2/sex/litter from each treatment group were fed control or DEET diets for a 9-month maintenance period. Then 20 litters from each group (1/sex) were randomly selected for a neurotoxicity assessment conducted over a period of 8 weeks. Neurotoxicity evaluations included: Functional Observational Battery, motor activity, passive avoidance, M-Maze and acoustic startle response tests, histopathology of nervous tissues. **9-Month Maintenance period** **≥ 38 mg/kg bw/day:** ↓bw (♀). **≥ 152 mg/kg bw/day:** ↓bw (♂). **378 mg/kg bw/day:** ↓fc (♀). **Neurotoxicity Assessment following 9-Month Maintenance period** **≥ 38 mg/kg bw/day:** ↓bw (♂/♀). **≥ 152 mg/kg bw/day:** ↓fc (♀). **378 mg/kg bw/day:** ↑horizontal activity, ↑distance travelled (♀). **Evidence of neurotoxicity** **Limitations**: No positive control data were provided. High variability was noted in the motor activity and auditory startle response (ASR) assessments. Individual data were not provided for the ASR and water maze assessments. Motor activity was assessed at a single time point only. The criterion used for task acquisition in the water maze (M-maze) was not clear therefore making the interpretation of the available

Study type/ Animal/PMRA No.	Study results
	data was challenging. Brain morphometric analysis not conducted.
30-Day Dermal Neurotoxicity Toxicity Non-Guideline Sprague-Dawley rat In vitro Neural Cell Viability Sprague-Dawley rat primary cortical neurons and astrocytes PMRA No. 3225516	**Acceptable with limitations** **In vivo experiment assessing arousal (open field test), locomotion, habituation, and motor coordination (open field test and ladder test):** **40 mg/kg bw/day**: Following 30 days of dermal exposure, DEET was still detectable in the plasma 24 hrs after the last application. DEET was also detected in the liver and brain samples. Levels in the liver were significantly higher than in the brain. No treatment-related effects were observed in the assessed neurobehavioral parameters. **In vitro experiment assessing viability of primary cortical neurons and astrocytes following 7 days incubation with DEET:** **≥ 1 µg/mL:** ↓ neuron survival after 7 days of treatment. No effects on astrocytes. **Limitations:** Low number of animals (5/sex/group) and a single dose level was tested. Lack of information for the in vivo dermal dosing methods. The test substance was not characterized; however, it was a commercially purchased analytical standard.
In Vitro Cholinesterase Inhibition Non-Guideline Swiss-Webster mouse phrenic hemidiaphragm muscles PMRA No. 3248567	**Acceptable with limitations** **500 µM:** prolonged the decay time constant of synaptic potentials of endplate regions of the muscle fibre by threefold compared to the control group. However, higher concentrations of DEET were required to prolong the decay time constant of synaptic events of mammalian neuromuscular preparations (500 µM) compared to cockroach synaptic preparations (1 µM), suggesting that synaptic preparations from insects are more sensitive to DEET relative to mammalian synaptic preparations. Cholinesterase inhibition: Incubation of AChE and BuChE with DEET (1-10 mM) and the substrate resulted in a reduction of enzyme activity. DEET is capable of inhibiting the hydrolysis of acetylthiocholine and butyrylthiocholine. The preincubation of the enzyme with DEET in the absence of the substrate did not change the extent of the inhibition, and dilution of the inhibited enzyme restored enzyme activity, suggesting that DEET can be considered a reversible inhibitor of cholinesterase.

Study type/ Animal/PMRA No.	Study results
	Limitations: The individual data was not provided, and only one concentration was assessed.
In Vitro Cholinesterase Study Non-Guideline Human erythrocyte acetylcholinesterase PMRA No. 3607658	**Acceptable with limitations** **≥ 100 uM:** ↓BuChE activity. **≥ 1000 uM:** ↓AChE activity. Cholinesterase inhibition by DEET was completely reversible and had complete recovery of enzyme activities. **Limitations:** The individual data was not provided, and the test substance was not characterized; however, it was a commercially purchased analytical standard.
In Vitro Cholinesterase Inhibition and Effects on Na and K Channels Non-Guideline Recombinant human AChE, rat cortical neurons PMRA No. 3248574	**Acceptable with limitations** Human AChE inhibition: DEET is a poor inhibitor of AChE, with less than 10% inhibition (IC_{50} = 12 mM, [7-17 mM]). Patch clamp of rat cortical neurons: DEET blocked both Na and K channels. DEET blocked inward Na currents at 1 mM, and the effect could be washed out to restore approximately 50% of the Na current amplitude. DEET-mediated K channel block was concentration-dependent. DEET blockage was capable of being washed out to restore approximately 50% of the control current amplitude. K channels were more sensitive to DEET compared to Na channels as they were blocked with an EC_{50} that was 6-fold lower. **Limitations:** Individual data was not provided.
Additional non-guideline studies	
Acute Oral Toxicity (presumed gavage) Non-guideline Wistar rats PMRA No. 3225522	**Acceptable with limitations** **947 mg/kg bw:** ↑liver wt **Limitations:** Only one dose and six animals were tested, the test substance was delivered in olive oil, so it is presumed to have been gavage administration; however, this was not clearly stated, and the individual data were not provided. The test substance was not characterized; however, it was a commercially purchased analytical

Study type/ Animal/PMRA No.	Study results
	standard.
Acute Oral Toxicity (gavage) Non-Guideline Wistar rat PMRA No. 3225507	**Acceptable with limitations** **474 mg/kg bw:** ↓GSH in the kidney, ↑noradrenaline, pneumonic changes to the lung, interstitial fibrosis, congestion, and inflammation to the lung. **Limitations:** The study author only tested six animals per group, mixed the sexes of the animals, only one dose was tested, and individual values were not provided.
Acute Dermal Toxicity Non-Guideline Sprague-Dawley rat PMRA No. 3225123	**Acceptable with limitations** **400 mg/kg bw:** ↑urinary 8-OHdG. **Limitations:** Only five animals and a single dose were tested. Individual data not provided.
Acute Dermal Toxicity Non-Guideline Sprague-Dawley rat PMRA No. 3225149	**Acceptable with limitations** **400 mg/kg bw:** ↑urinary 3-nitrotyrosine 24 hrs PD. **Limitations:** Only five animals and a single dose were tested. Individual data not provided.
90-Day Oral Toxicity Investigation of Kidney Effects (diet) – Non-Guideline Sprague-Dawley, Fischer 344 and NBR rat (♂) PMRA No. 1171188	**Acceptable with limitations** **Sprague-Dawley rats** (known high producer of alpha 2u-globulin): **400 mg/kg bw/day:** Renal cast formation (granular), presence of regenerative tubules in the renal cortex and chronic inflammation in the renal cortex and presence of hyaline droplets in kidneys. **Fischer 344 rats** (known high producer of alpha 2u-globulin): **400 mg/kg bw/day:** Tubular regeneration (slightly lower severity relative to Sprague-Dawley rats), inflammation of the renal cortex. Both control and treatment group had hyaline droplets. **NBR rats** (known non-producer of alpha 2u-globulin): **400 mg/kg bw/day:** ↑rel kidney wt. **Limitations:** Only one dose level tested.
90-Day Dermal Toxicity Effects of Castration on Renal	**Acceptable with limitations** **Castrated rats:**

Study type/ Animal/PMRA No.	Study results
Toxicity Non-Guideline Sprague-Dawley rat PMRA No. 1237516	**1000 mg/kg bw/day:** very slight erythema, anogenital staining, ↓bw, ↑kidney wt, ↑hyaline droplet, inflammation, regeneration, positive for hyaline droplets Mallory-Heidenhain staining, positive for alpha 2u-globin via immunocytochemistry; however, microscopic incidences and severity were lower relative to non-castrated rats. **Non-castrated rats:** **1000 mg/kg bw/day:** very slight erythema, anogenital staining, ↑kidney wt, hyaline cast, hyaline droplet, inflammation, regeneration, granular cast, positive for hyaline droplets Mallory-Heidenhain staining, positive for alpha 2u-globin via immunocytochemistry. Microscopic findings were observed in almost all non-castrated rats. Castration lessened but did not prevent the formation of renal lesions characteristics of alpha 2u-globulin. **Limitations:** Only one dose tested.
Assessment of Cell Viability on Human Cells after Treatment with DEET in vitro Non-Guideline BE(2)-M17 cells (human neuroblast) PMRA No. 3607649	**Acceptable with limitations** EC_{50} values: at 4 hrs = 869.3 mg/L; 12 hrs = 1124.6 mg/L; 24 hrs = 778.2 mg/L; 48 hrs = 495.7 mg/L. DEET was cytotoxic to BE(2)-M17 cells at the EC_{50} values listed above. ↑ Cytotoxicity with exposure duration. DEET did not affect the morphological characteristics BE(2)-M17 cells at concentrations up to 50 mg/L. Shrunken cells were observed at concentrations of 500 and 750 mg/L, and ↓cell numbers was observed. **Limitations:** The individual data was not provided, the individual concentrations tested were not provided (seven concentrations were determined by the figures), and the test substance was not characterized; however, it was commercially purchased analytical standard.

Study type/ Animal/PMRA No.	Study results
In vitro Mode of Action Investigations Non-Guideline Human umbilical venous endothelial cells (HUVEC), mouse endothelial cells (ECs), human embryonic kidney 293 cells, U87MG glioblastoma-astrocytoma cells, B16F10 melanoma cells PMRA No. 3607698	**Acceptable with limitations** DEET did not ↑proliferation of cancer U87MG cells, but enhanced HUVEC proliferation when compared with non-treated cells. No effect on the proliferation of B16F10 tumor cell line was observed. Additionally, no cytotoxic or pro-apoptotic effects were observed in cells treated with DEET. DEET treatment ↑ capillary length formation in HUVEC. No significant difference in in vitro pro-angiogenic effects of HUVECs treated with DEET. pFHHSiD (selective M3 muscarinic receptor antagonist) completely prevented the proliferative properties of DEET, and prevented DEET from ↑ capillary length, indicating that DEET may be promoting angiogenesis through a pathway sensitive to a selective antagonist of M3 receptor or M3 SiRNA. ↓endothelial AChE activity compared to the control group. ↑endothelial cell migration, ↑adhesion; however, these two effects were prevented by pFHHSiD. ↑phosphorylation of focal adhesion kinase; however, pFHHSiD prevented phosphorylation. ↑endothelial NO production in HD only, ↑ eNOS phosphorylation on the activator site, ↓at the inhibitor site, ↑VEGF expression, and this was prevented with pFHHSiD. **Conclusion:** The in vitro studies demonstrated that DEET can inhibit endothelial AChE activity. Additionally, DEET was found to act as an allosteric modulator of M3 muscarinic receptor. **Limitations:** The individual data was not provided, and the test substance was not characterized; however, it was a commercially purchased analytical standard. Additionally, only two doses were assessed.

Appendix IV Non-occupational exposure and risk assessment

Table 1 Episodic (acute) postapplication hand-to-mouth assessment for children

Formulation	Application rate[a] (mg product/cm^2)	F_{AI}[b]	HR[c] (mg/cm^2)	HtM events (#/hr)	Oral exposure[d] (mg/kg bw/day)	Oral MOE[e] (Target = 100)
Aerosol, PP, towelette	1.1	10%	0.11	14	0.195	260
Pump spray	0.62		0.062		0.110	450
Lotion	2.0		0.20		0.355	140

F_{AI} = concentration of active ingredient in the product; PP = pressurized product; MOE = margin of exposure; BW = body weight; HtM = hand-to-mouth; hr = hour

[a] Standard values from the Residential SOPs (USEPA, 2012) based on insect repellent efficacy studies and are formulation-specific.

[b] Highest concentration of DEET in products approved for application to children under 12 years old.

[c] Hand residue (HR) was calculated as a product of the application rate and concentration of DEET in products (F_{AI})

[d] Oral exposure (mg/kg bw/day) = [HR × F_m × SA_H × # of apps (1) × (1-(1-SE)$^{ET \times FreqHtM / \#Apps\ (1)}$)] /BW. The following point estimates from the USEPA Residential SOPs (2012) were used to calculate oral exposure: HR is the resides on the hand; fraction mouthed (F_m) is the fraction of hand surface area mouthed per event (0.13); SA_H is the surface area of the hands (150 cm^2); the saliva extraction factor (SE) was 0.48; frequency of hand-to-mouth events per hour (FreqHtM) was 14; exposure times (ET) was 3.5 hours; and the body weight for children (1<2 years) was 11 kg.

[e] MOE = NOAEL/ oral exposure. The NOAEL of 50 mg/kg bw is based on an acute oral neurotoxicity study in rats. The target MOE is 100.

Table 2 Estimated DEET intermediate-term exposure and risk for urinary DCBA excreted for each exposure group

Exposure group[a]	DCBA (µg/L) [b]	Urine excretion (L/day)[c]	Fue[d]	Dermal exposure (mg/kg bw/day)[e]	MOE (Target = 100)[f]
Low	6854	0.82	0.314	0.44	690
Medium	19,268			1.23	250
Upper	41,260			2.63	110

DCBA = 3-diethylcarbamoyl benzoic acid (primary metabolite of DEET); bw = body weight; Fue = urinary excretion fraction; admin = administered dose; MOE = margin of exposure

[a] Exposure groups were based on the amount of DEET applied during the study monitoring period. Determined by the study authors.

[b] Geometric mean urine concentrations for urine samples collected for each child in each exposure group.

[c] Volume of urine excreted per day. Determined using the urine flow rate of 20 mL/kg-day for children, extrapolated for the average body weight of children in the study (41 kg).

[d] Urinary excretion fraction, used to estimate the amount of DCBA excreted as a result of an administered dermal dose of DEET.

[e] Dermal exposure estimated from the urine concentration of DCBA. Dermal exposure (mg/kg bw/day) = DCBA excreted (µg/L) × urine excreted per day (L/day)/ (Fue × BW × 1000 µg/mg). Average body weight for the children in the biomonitoring study was 41 kg.

[f] MOE = NOAEL/ oral exposure. The NOAEL of 300 mg/kg bw/day is based on a 90-day dermal toxicity study in rats. The target MOE is 100.

Table 3 Estimated DEET intermediate-term exposure and risk for urinary DCBA excreted with time following DEET application

Time period (hours since application)	DCBA (µg/L)[a]	Urine excretion		DCBA (µg)		Fue[f]	Dermal exposure (mg/kg bw/day)[g]	MOE (Target = 100)[h]
Time period	Time period	L/day[b]	L/time period[c]	Time period[d]	Day[e]			
>2–≤8	12 102	0.82	0.205	2481	11 410	0.314	0.89	340
>8–≤14	16 635			3410				
>14–≤20	14 522			2977				
>20–≤28	12 406			2543				

DCBA = 3-diethylcarbamoyl benzoic acid (primary metabolite of DEET); bw = body weight; Fue = urinary excretion fraction; MOE = margin of exposure

a Geometric mean urine concentrations for urine samples collected in each of the time periods since DEET application.

b Volume of urine excreted per day. Determined using the urine flow rate of 20 mL/kg-day for children, extrapolated for the average body weight of children in the study (41 kg).

c Volume of daily urine excreted per 6 hour time period. Determined by assuming equal excretion of urine throughout the day.

d Estimated DCBA excreted in urine for each time period. Determined by multiplying the DCBA excreted per time period (µg/L) by the urine excreted per time period (L/time period).

e Estimated daily excretion of DCBA per day. Determined by summing the amount of DCBA (µg) excreted per time period.

f Urinary excretion fraction, used to estimate the amount of DCBA excreted as a result of an administered dermal dose of DEET.

g Dermal exposure estimated from the urine concentration of DCBA. Dermal exposure (mg/kg bw/day) = DCBA excreted per day (µg)/ (Fue × BW × 1000 µg/mg). Where BW = body weight. Average body weight for the children in the biomonitoring study was 41 kg.

h MOE = NOAEL/ oral exposure. The NOAEL of 300 mg/kg bw/day is based on a 90-day dermal toxicity study in rats. The target MOE is 100.

Appendix V Environmental assessment

Table 1 Toxicity of DEET to non-target aquatic species

DACO – Title	PMRA#	Reference	Endpoint	Classification
9.3.2 Acute daphnia sp.	3668006	Kumar, 2004 in Weeks et al., 2011	48-h EC_{50} = 34.4 mg/L	Slightly toxic
	3668006 3668001	Forbis and Burgess, 1985 in Weeks et al., 2011; USEPA 2012	48-h EC_{50} = 75 mg/L	Slightly toxic
	3667998	Seo et al., 2005	48-h LC_{50} = 160	Practically non-toxic
	3667983	ATSDR, 2017	51-h LC_{50} = 75 mg/L	Slightly toxic
	3667998	Seo et al., 2005	48-h LC_{50} = 160 mg/L 96-h LC_{50} = 108 mg/L	Practically non-toxic
	3667982	Aronson et al., 2011	48-h EC_{50} = 34.4 mg/L	Slightly toxic
9.3.3 Chronic daphnia sp.	3668006 3667983	Minderhout et al. 2008 in Weeks et al., 2011; ATSDR, 2017	21-d NOEC = 14 mg/L (reproduction)	N/A
	3667982	Aronson et al., 2011	21-h NOEC = 26 mg/L immobility 21-h NOEC = 3.7 mg/L length reduction 21-h NOEC = 14 mg/L reproduction	N/A
9.3.4 Other freshwater invertebrates	Book, not uploaded	Mayer and Ellersieck, 1986	Amphipod Gammarus fasciatus 96-h LC_{50} >100 mg/L	Practically non-toxic
	3668005	Von Elert et al., 2006	NOEC >0.044 mg/L	Unclear
9.4.2 Acute marine crustacean	-	-	No data	-
9.4.4 Acute marine mollusk	-	-	No data	-

DACO – Title	PMRA#	Reference	Endpoint	Classification
9.4.5 Chronic marine invertebrate	-	-	No data	-
9.4.8 Bioconcentration (bivalve or crustacean)	2937037	DeSolla et al, 2016	BAF = 8.91	N/A
9.5.2.1 Acute cold water fish	3668001 3667983	USEPA, 2012; ATSDR, 2017	Rainbow trout 96-h LC_{50} = 75 mg/L	Slightly toxic
9.5.2.3 Acute freshwater fish	3667986	Brooke et al, 1984	Fathead minnow 96-h LC_{50} = 110 mg/L	Practically non-toxic
	3667997	Michael and Grant, 1974	Western mosquitofish (Gambusia affinis) 48-h LC_{50} = 235 mg/L	Practically non-toxic
	3668005	Von Elert et al., 2016	NOEC > 0.044 mg/L	Unclear
9.5.6 Bioaccumulation	3669001	USEPA, 2012	BAF = 22 L/kg (Regression w/log K_{ow}) 13.3 (EPI Suite v4.10)	N/A
	3667983	ATSDR, 2017	BAF = 0.8-2.4 L/kg carp (taken from CITI 1992; Weeks et al., 2012)	N/A
	3668006	Weeks et al., 2011	BAF = 0.8 to 2.4 L/kg carp	N/A
9.8.2 Freshwater algae	3668006	Desjardins et al., 2002 in Weeks et al., 2011	Green algae (*Selenastrum capricornutum)* *96-h ECb50* = 18 mg a.i./L	N/A
	3667983	ATSDR, 2017 (using Desjardin et al., 2002)	Green algae (*Selenastrum capricornutum*) 96-h ECr50 = 43 mg a.i./L	n/a
	3668006	Rao, 2003 in Weeks et al., 2011	Green algae (*Selenastrum capricornutum*)	n/a

DACO – Title	PMRA#	Reference	Endpoint	Classification
			72-h ECb50 = 51 mg a.i./L	
	3667983	ATSDR, 2017 (using Rao, 2003)	Green algae (*Selenastrum capricornutum*) 72-h ECr50 = 100 mg a.i./L	n/a
	3667982	Aronson et al., 2011	Green algae (*Pseudokirchneriella subcaptitata*) 96-h ECg50 = 4.1 mg/L	n/a
	3667988	Costanzo et al., 2007	Green algae (*Chlorella protothecoides*) 24-h EC50 = 388 mg/L	n/a

Appendix VI Proposed label amendment for products containing DEET

The proposed label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements below.

1.0 Label amendments for DEET technical products

PCPA Reg. No. 18068
The active ingredient statement on the label must be revised to:

ACTIVE INGREDIENT:
DEET (N,N-Diethyl-m-toluamide) … 98.97%
Related active toluamides … 0.15%

For technical grade active ingredients:

The following signal word and hazard statements should appear on the principal display panel of the label:

- The signal word "WARNING"
- The skull and crossbones symbol in an inverted triangle border shape (see image below) should appear on the principal display panel in close proximity to the hazard statement "POISON"

- The following hazard statements should appear on the label: "EYE AND SKIN IRRITANT"

On the secondary display panel, ensure the following statements are included in the PRECAUTIONS section:

- "Harmful if swallowed. Causes eye irritation. **DO NOT** get in eyes. May irritate the skin. Avoid contact with skin."

In the FIRST AID section, ensure the following statements are included:

FIRST AID	
If swallowed	Call a poison control centre 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 centre or doctor. Do not give anything by mouth to an unconscious person.
If on skin or clothing	Take off contaminated clothing. Rinse skin immediately with plenty of water for 15–20 minutes. Call a poison control centre or doctor for treatment advice.

FIRST AID	
If in 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 centre or doctor for treatment advice.
	Take container, label or product name and P.C.P. Registration Number with you when seeking medical attention.

2.0 Label amendments for DEET domestic-class end-use products

The required label statements for end-use products from the previous re-evaluation (RRD2002-01) continue to be required, unless they are superseded by the statements below.

The following label improvements are proposed for all DEET end-use products on the FRONT PANEL of the product label:

- Products containing **≤ 10% DEET**:
  - In a boxed enclosure, add "**DO NOT** USE ON INFANTS UNDER 6 MONTHS OF AGE".
- Products containing **>10% DEET**:
  - In a boxed enclosure, add "**DO NOT** USE ON CHILDREN 12 YEARS OF AGE AND UNDER".

The following label improvements are proposed for all DEET end-use products under PRECAUTIONS:

- All products, must contain precautionary label statements such as:
  - "**DO NOT** get into eyes"
  - "**DO NOT** spray directly to face"
  - "Avoid contact with eyes during application"
- All products, must add the following precautionary label statement:
  - "Skin reactions (e.g., itchy skin, rash) may occur in rare cases"
- Products containing **≤ 10% DEET**, must be revised, as follows:
  - **Remove:** "avoid application to hands"
  - **Add:** "Avoid application to children's hands"
- Products containing **> 10% DEET**, must contain precautionary label statements such as:
  - "**DO NOT** allow children (12 years of age and under) to handle this product."
  - "**DO NOT** use on children (12 years of age and under)'
- Products that have the potential to be flammable or may damage synthetic, plastic or painted surfaces, must contain label statements, warning the consumer of the noted physical and chemical hazard . For example -
  - FLAMMABLE: statements must be revised, as follows:
    - Add all required statements regarding flammability related to the product, if required and not currently present.
    - **Remove** : "Keep treated surfaces away from fire or open flame until dry."
    - **Add**: "Keep treated surfaces, includes skin or clothing, away from fire or open flame until dry."

- **Remove**: all variations of the following statement "Do not apply on or near acetate, rayon, or other synthetic fabrics, plastics, watch crystals, leather, painted or varnished surfaces including automobiles. May damage synthetic surfaces and other finishes."
- **Add**: "**DO NOT** APPLY ON OR NEAR: acetate, rayon, or other synthetic fabrics, plastics, watch crystals, leather, painted or varnished surfaces including automobiles. May damage synthetic surfaces and other finishes."

The following statements are proposed for all DEET end-use products under DIRECTIONS for USE:

- Products containing **≤ 10% DEET**, must contain clear directions of use statements, such as:
  - "**DO NOT** apply to children's hands."
  - "**DO NOT** allow children to handle this product."
  - "When using on children, apply to your own hands and then put it on the child."
- Products containing **> 10% DEET**, must contain clear directions of use statements, such as
  - **"**When using on children (older than 12 years), apply to your own hands and then put it on the child."
- All products must contain clear best practice statements, such as:
  - "**DO NOT** apply over cuts, wounds, irritated or sunburned skin."
  - "After returning indoors, wash treated skin with soap and water."
  - "Remove and wash treated clothing before wearing it again."

References

A. Information considered in the updated chemistry assessment

List of studies/information submitted by registrant

PMRA document number	Reference
1469804	Technical Chemistry file - DTU1. DEET analytical information for 5 different lots - Certificate of Analysis, GC Addendum Analysis and GC Curve. DACO 2.13
1779037	Description of Starting Materials. DACO 2.11.2
1779038	2009. Detailed Production Process Description, DACO: 2.11.3
1940386	2010. Flow Chart for proposed revised manufacturing of DEET insect repellent. DACO 2.11.3
2744375	2017. N,N-Diethyl-M-Toluamide, Part 2.11: Manufacturing Methods for the TGAI. DACO 2.1,2.11,2.12.1,2.13.1,2.13.3,2.2
1902248	2010. Preliminary Analysis. 2.13.3
2744375	2017. N,N-Diethyl-M-Toluamide, Part 2.11: Manufacturing Methods for the TGAI. DACO 2.1,2.11,2.12.1,2.13.1,2.13.3,2.2

B. Information considered for the updated toxicological assessment

Studies/information submitted by registrant

PMRA document number	Reference
1126612	1991, Addendum to Report Entitled “Pharmacokinetics and Comparative Dermal Absorption Study of N, N-Diethyl-M-Toluamide (DEET) in the Rat. DACO: 4.5.12.
1126611	1990, Determination of Expired 14C Volatiles Following a Single Oral or Dermal Dose of N, N-Diethyl-M-Toluamide (DEET) in the Rat. DACO: 4.5.12.
1176459	1998, Blood Level Study in Rats Following a Single Oral Bolus Administration of N,N-Diethyl-m-Toluamide (DEET). DACO: 4.5.12.
1190674	1999, 48-Hour Blood Level Study in Rats Following Single Oral Bolus Administration of N,N-Diethyl-M-Toluamide (DEET). DACO 4.5.12.
1176460	1998, Blood Level Study in Rats Following Single and Repeated Dermal Applications of N,N-Diethyl-m-Toluamide (DEET). DACO: 4.5.12.
1176461	1997, Blood Level Study in Dog Following Oral Administration, via Gelatin Capsules, of N,N-Diethyl-m-Toluamide (DEET). DACO: 4.5.12.
2934207	1999, A Study to Determine the Half-Life and Volume of Distribution of N,N-Diethyl-m-Toluamide (DEET) when Administered by a Single Intravenous Injection in Two Beagle Dogs. DACO: 4.5.12.
1176463	1997, A Blood Level Study in Humans Following Topical Application of N,N-Diethyl-m-Toluamide (DEET). DACO: 4.5.12.

PMRA document number	Reference
1466105	2000, Acute Oral Toxicity Test with DEET Insect Repellent. DACO: 4.2.1.
2934211	2001, Acute Oral Toxicity Study in Rats – Defined LD_{50}. DACO: 4.2.1.
1466103	2000, Acute Dermal Toxicity Limit Test with DEET Insect Repellent. DACO: 4.2.2.
2934212	2001, Acute Dermal Toxicity Study in Rats - Limit Test. DACO: 4.2.2.
1413431	2000, Acute Dermal Toxicity Limit Test with DEET Insect Repellent. DACO: 4.2.2.
1139202	1979, Behavioral Effects of Acute Aerosol Exposure to N,N-Diethyl-Meta-Toluamide (M-DET). DACO: 4.2.3.
2934213	2001, Acute Inhalation Toxicity Study in Rats – Limit Test. Repellent. DACO: 4.2.3.
2934214	2001, Primary Eye Irritation Study in Rabbits. DACO: 4.2.4.
2934203	2000, Primary Eye Irritation Test with DEET Insect Repellent. DACO: 4.2.4.
1467112	1985, Primary Dermal Irritation Study in Albino Rabbits. DACO: 4.2.5.
2934215	2001, Primary Skin Irritation Study in Rabbits. DACO: 4.2.5.
2934216	2001, Dermal Sensitization Study in Guinea Pigs (Buehler Method). DACO: 4.2.6.
2934205	2000, Dermal Sensitization Study in Guinea Pigs (Buehler Method) with DEET Insect Repellent. DACO: 4.2.6.
1237518	1988, Evaluation of DEET in a Two Week Dose Range Finding Study in Hamsters. DACO: 4.3.8.
1237501	1989, Evaluation of DEET in a 90-Day Dose Range Finding Study in Hamsters. DACO: 4.3.8.
1237517	1987, Evaluation of DEET in a 90-Day Oral Dose Range Finding Study in Mice. DACO: 4.3.8.
1237502	1987, Evaluation of DEET in a 90-Day Oral Dose Range Finding Study in Rats. DACO: 4.3.8.
1163662	1994, Evaluation of DEET in a Two-Week Palatability Study in Dogs. DACO: 4.3.1.
1163663	1994, Evaluation of DEET in a Two-Week Oral Gelatin Capsule Toxicity Study in Dogs. DACO: 4.3.1.
1163665	1994, Evaluation of DEET in a Three Week Toxicity Study in Dogs. DACO: 4.3.1.
1163666	1995, Evaluation of DEET in an Eight Week Dietary Toxicity Study in Dogs. DACO: 4.3.1.
2934217	1997, Evaluation of DEET in a Eight-Week Oral Toxicity Study in Dogs. DACO: 4.3.3.
1163661	1995, Evaluation of DEET in an Eight-Week Oral Gelatin Capsule Toxicity Study in Dogs. DACO: 4.3.1.
1163660	1994, Evaluation of DEET in a One-Year Chronic Oral Toxicity Study in Dogs. DACO: 4.4.1.
1237515	1987, Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Rats. DACO: 4.3.4.

PMRA document number	Reference
1171189	1991, Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Micropigs. DACO: 4.3.4.
1237510	1990, Evaluation of DEET in an Eighteen Month Dietary Oncogenicity Study in Mice. DACO: 4.4.2.
1163674	1995, Evaluation of DEET in a Two-Year Dietary Toxicity and Oncogenicity Study in Rats. DACO: 4.4.1, 4.4.2.
1237504	1989, Evaluation of DEET in a Two Generation Reproduction/Fertility Study in Rats. DACO 4.5.1.
1237505	1989, Developmental Toxicity Dose Range-Finding Study of DEET Administered by Gavage to CD (Sprague-Dawley) Rats. DACO: 4.5.2.
1237506	1990, Developmental Toxicity Evaluation of DEET Administered by Gavage to CD (Sprague-Dawley) Rats. DACO: 4.5.2.
1139193	1992, Developmental Toxicity Dose Range-Finding Study of DEET Administered by Gavage to New Zealand White Rabbits. DACO: 4.5.2.
1126607	1991, Developmental Toxicity Evaluation of DEET Administered by Gavage to New Zealand White Rabbits. DACO: 4.5.2.
1237507	1989, Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay. DACO: 4.5.4.
1237509	1989, Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with a Confirmatory Assay. DACO: 4.5.4.
1237508	1989, Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. DACO: 4.5.4.
2934206	1993, CHO/HGPRT Forward Mutation Assay. DACO: 4.5.5.
1237530	1990, Neurotoxicity Evaluation in Rats Following Acute Oral Exposure to DEET. DACO: 4.5.10.
1171190	1997, DEET Nine-Month Feeding Protocol in Rats. DACO: 4.5.12.
1237541	1990, Neurotoxicity Evaluation in Rats Following Multigeneration Exposure to DEET. DACO: 4.5.11.
1209941	1980, The Effect of DEET (N,N-Diethyltoluamide) on the Morphology, Viability, and Count of Sperm in Rats Exposed by Dermal Administration. DACO: 4.5.1.
1171188	1992, Evaluation of DEET in a Multistrain 90-Day Dietary Renal Toxicity Study in Rats. DACO: 4.3.8.
1237516	1989, Evaluation of DEET in a 90-Day Dermal Toxicity Study in Castrated Male Rats. DACO: 4.3.4.

Additional information considered

Published information

PMRA document number	Reference
3248577 3683143	Blomquist L, Thorsell W., 1977. Distribution and fate of the insect repellent 14C-N, N-diethyl-m-toluamide in the animal body. II. Distribution and excretion after cutaneous application. Acta Pharmacol Toxicol (Copenh);41(3): 235-43. DACO 4.9.
3607611	Garud A et al., 2011. Acute Toxicity Studies of Safer and More Effective Analogues of N,N-Diethyl-2-Phenylacetamide. J Med Entomol.: 48(6): 1160-6. DACO 4.8
2246887 3683204	Selim S, Hartnagel RE Jr, Osimitz TG, Gabriel KL, Schoenig GP., 1995. Absorption, metabolism, and excretion of N,N-diethyl-m-toluamide following dermal application to human volunteers. Fundam Appl Toxicol.; 25(1):95-100. DACO 5.8,10.3.2
3607721	Barr, D et al., 2010. Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey. Sci Total Environ.; 408(4): 790-5. DACO 4.8
3607732	Zhao, X et al., 2024. A prospective cohort study of exposure to household pesticide with cardiovascular diseases mortality in older adults. J Hazard Mater.; 471:134316. DACO 4.8
3607701	Yan, S et al., 2022. Exposure to N,N-diethyl- m-toluamide and cardiovascular diseases in adults. Front Public Health.;10:922005. DACO 4.8
3607706	Segal TR, et al., 2017. Urinary concentrations of 3-(diethylcarbamoyl)benzoic acid (DCBA), a major metabolite of N,N-diethyl-m-toluamide (DEET) and semen parameters among men attending a fertility center. Hum Reprod.; 32(12): 2532-2539. DACO 4.8
3607707	Haleem, Z et al., 2020. Exposure to N,N-Diethyl-Meta-Toluamide Insect Repellent and Human Health Markers: Population Based Estimates from the National Health and Nutrition Examination Survey. Am J Trop Med Hyg.; 103(2):812-814. DACO 4.8
3607714	Swan, S et al., 2003. Semen quality in relation to biomarkers of pesticide exposure. Environ Health Perspect.; 111(12): 1478-84. DACO 4.8
3607699	Chronister, B et al., 2023. Urinary Glyphosate, 2,4-D and DEET Biomarkers in Relation to Neurobehavioral Performance in Ecuadorian Adolescents in the ESPINA Cohort. Environ Health Perspect.; 131(10):107007. DACO 4.8
3607719	Wickherham, E et al., 2012. Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants. Environ Int.; 47:80-5 DACO 4.8
3607730	Cui, Q et al., 2022. Association of N,N-diethyl-m-toluamide (DEET) with obesity among adult participants: Results from NHANES 2007-2016. Chemosphere; 307(Pt 1):135669. DACO 4.8
3607739	Addissie, Y et al., 2020. Prenatal exposure to pesticides and risk for holoprosencephaly: a case-control study. Environ Health; 19(1):65. DACO 4.8

PMRA document number	Reference
3607612	Usmani, K et al., 2002. In vitro human metabolism and interactions of repellent N,N-diethyl-m-toluamide. Drug Metab Dispos.; 30(3): 289-94. DACO 4.8
3607624	Abu-Qare, A & Abou-Donia, M 2008. In vitro metabolism and interactions of pyridostigmine bromide, N,N-diethyl-m-toluamide, and permethrin in human plasma and liver microsomal enzymes. Xenobiotica.; 38(3):294-313. DACO 4.8
3607639	Yeung, J & Taylor, W 1988. Metabolism of N,N-diethyl-m-toluamide (DEET) by liver microsomes from male and female rats. Simultaneous quantitation of DEET and its metabolites by high performance liquid chromatography. Drug Metab Dispos.; 16(4): 600-4. DACO 4.8
3225522	Magesh A, ET AL., 2018. Sivanesan S, Rajagopalan V, Geetha RV, Roy A. Safety Evaluation of Various Vector Repellents in Combination with Deltamethrin in Wistar Rats. J Pharm Bioallied Sci.; 10(1): 21-28. DACO 4.8
3225123	Abu-Qare, A & Abou-Donia, M 2000. Increased 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative DNA damage in rat urine following a single dermal dose of DEET (N, N-diethyl-m-toluamide), and permethrin, alone and in combination. Toxicol Lett.; 117(3):151-60. DACO 4.8
3225149	Abu-Qare et al., 2001. Induction of urinary excretion of 3-nitrotyrosine, a marker of oxidative stress, following administration of pyridostigmine bromide, DEET (N,N-diethyl-m-toluamide) and permethrin, alone and in combination in rats. Toxicol Lett.; 121(2):127-34. DACO 4.8
3225507	Anitha, M et al., 2019. Oxidative stress and neuromodulatory effects of deltamethrin and its combination with insect repellents in rats. Environ Toxicol.; 34(6):753-759. DACO 4.8
3225204	Tisch, M et al., 2002. Genotoxicity studies on permethrin, DEET and diazinon in primary human nasal mucosal cells. Eur Arch Otorhinolaryngol.; 259(3): 150-3. DACO 4.8
3607649	Kim et al., 2011. The effect of environmental micropollutant (DEET) on the expression of cell cycle and apoptosis regulatory proteins in human cells. Biotech and Bioprocess Eng; 16, 400–406. DACO 4.8
3607698	Legeay, S et al., 2016. The insect repellent N,N-diethyl-m-toluamide (DEET) induces angiogenesis via allosteric modulation of the M3 muscarinic receptor in endothelial cells. Sci Rep.; 6:28546 DACO 4.8
3248567	Corbel, V et al., 2009. Evidence for inhibition of cholinesterases in insect and mammalian nervous systems by the insect repellent deet. BMC Biol.; 7:47. DACO 4.8
3607658	Wille , T et al., 2011. In vitro kinetic interactions of DEET, pyridostigmine and organophosphorus pesticides with human cholinesterases. Chem Biol Interact.; 190(2-3):79-83. DACO 4.8
3248574	Swale, D et al., 2014. Neurotoxicity and mode of action of N, N-diethyl-meta-toluamide (DEET). PLoS One.; 9(8):e103713. DACO 4.8
3225516	Fediuk, DJ et al., 2011. Tissue disposition of the insect repellent DEET and the sunscreen oxybenzone following intravenous and topical administration in rats. Biopharm Drug Dispos.; 32(7): 369-79. DACO 4.8

PMRA document number	Reference
3225533	Zeiger, E et al., 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen.; 19 Suppl 21:2-141. DACO 4.8
3607712	Wei, C et al., 2023. Association between N, N-diethyl-m-toluamide exposure and the odds of kidney stones in US adults: a population-based study. Front Public Health; 11:1248674. DACO 4.8
3607726	Wu, R et al., 2023. Association of N, N-diethyl-m-toluamide (DEET) with hyperuricemia among adult participants. Chemosphere.; 338:139320. DACO 4.8
3637139	US EPA, 2014. DEET (N,N-Diethyl-meta-toluamide) Interim Registration Review Decision DACO 12.5.4
3637140	ECHA, 2010. Assessment Report - N,N-Diethyl-meta-toluamide (DEET) Product-type 19 DACO 12.5.4
3637142	ECHA, 2016. CLH report Proposal for Harmonised Classification and Labelling DACO 12.5.4
3656522	ECHA, 2010. N,N-Diethyl-meta-Toluamide (DEET) DACO 12.5.4

D. Information considered in the updated occupational and non-occupational assessment

Studies/information submitted by registrant

PMRA document number	Reference
1126609	1990. Human Use & Exposure To Insect Repellents Containing DEET. DACO 5.1
1190674	1999. 48-Hour Blood Level Study In Rats Following A Single Oral Bolus Administration Of N,N-Diethyl-M-Toluamide (DEET) In The Rat. DACO 4.5.12
1176459	1998. Blood Level Study In Rats Following A Single Oral Bolus Administration Of N,N-Diethyl-M-Toluamide (DEET). . DACO 4.5.12
1176460	1998. Blood Level Study In Rats Following Single And Repeated Dermal Applications Of N,N-Diethyl-M-Toluamide (DEET). DACO 4.5.12
1126611	1991. Determination Of Expired 14c Volatiles Following A Single Oral Or Dermal Dose Of N,N-Diethyl-M-Toluamine (DEET) In The Rat (Btc P01862;A490-0508). DACO 6.4
1176463	1997. A Blood Level Study In Humans Following Topical Application Of N,N-Diethyl-M-Toluamide (DEET). DACO 4.5.12
1126612	1992. Addendum + Report "Pharmacokinetics And Comparitive Dermal Absorption Study Of N,N-Diethyl-M-Toluamide (DEET) In The Rat. DACO 6.4
1171187	1992. Absorption And Mass Balance Of 14c-DEET After Topical Administration To Healthy Volunteers. DACO 4.2.9,6.4

Additional information considered

Published information

PMRA document number	Reference
3683167 3248577	Antonia M. Calafat et al., 2016, Environment International 92-93 (2016) 398-404, Novel exposure biomarkers of N,N-diethyl-m-toluamide (DEET): Data from the 2007-2010 National Health and Nutrition Examination Survey, DACO 5.7
3683143	Lars Blomquist and Walborg Thorsell, 1977, Acta pharmacol. et toxicol. 1977, 41, 235-243, Distribution and Fate of the Insect Repellent I4C-N,N-diethyl-mtoluamide in the Animal Body. 11. Distribution and Excretion after Cutaneous Application, DACO 4.8, 5.14
3683189	Robert J. Feldmann et al., 1970, The Journal of Investigative Dermatology, Vol 54, No. 5; 399-404, Absorption of Some Organic Compound Through the Skin in Man, DACO 5.8
3683194	A.D. Fraser et al., 1994, Journal of Analytical Toxicology, Vol. 19, May/June 1995, Analysis of Diethyltoluamide (DEET) Following Intentional Oral Ingestion of Muscol, DACO 4.8, 5.14
3682639	Jennifer C. Gibson et al, 2022, PLoS ONE, 17(8): e0268341, Development of an observational exposure human biomonitoring study to assess Canadian children's DEET exposure during protective use DACO 5.7
3682641	Jennifer C. Gibson et al., 2022, International Journal of Hygiene and Environmental Health 248 (2023) 114093, Biomonitoring of DEET and DCBA in Canadian children following typical protective insect repellent use. DACO 5.7
3685855	Rose McGready et al., 2001, American Journal of Tropical Medicine and Hygiene, 65(4), 2001, PP. 285-289, Safety of the Insect Repellent N, N-Diethyl-m-toluamide (DEET) in Pregnancy DACO 5.7
3685857	Sean M. Hays and Christopher R. Kirman, 2023, Regulatory Toxicology and Pharmacology 145 (2023) 105506, Biomonitoring Equivalents for N,N-Diethyl-meta-toluamide (DEET), DACO 4.8, 5.14
693639	Health Canada. 2002. Re-evaluation Decision Document RRD2002-01. Personal insect repellents containing DEET (N,N-diethyl-m-toluamide and related compounds). April 15, 2002.
	Health Canada. 2023. Canadian Biomonitoring Dashboard. Ottawa, ON. Available: https://health-infobase.canada.ca/biomonitoring/
3683197	Richard P. Moody et al., 2009, Journal of Toxicology and Environmental Health, Part A Current Issues, 26:2, 137-147, DOI: 10.1080/15287398909531240, Dermal absorption of the insect repellent deet (N,N- diethyl-m-toluamide) in rats and monkeys: Effect of anatomical site and multiple exposure DACO 5.8
3683195	R. P. Moody and B. Nadeau, 1993, Toxic. in Vitro Vol. 7, No. 2, pp. 167 176, 1993, An Automated In Vitro Dermal Absorption Procedure: III. IN Vivo and In Vitro Comparison with the Insect Repellent N,N-Diethyl-m-Toluamide in Mouse, Rat, Guinea Pig, Pig, Human and Tissue-Cultured Skin DACO 5.8

PMRA document number	Reference
3683199	Gerald P. Schoenig, 1995, Drug Metabolism and Disposition, 24(2):156-163, Absorption, Distribution, Metabolism and Excretion of N,N-DIETHYL-MTOLUAMIDE in the Rat DACO 4.8, 5.14
3683204 2246887	Sami Selim, 1995, Fundamental and Applied Toxicology 25, 95 - 100 (1995), Absorption, Metabolism, and Excretion of N-N-Diethyl-m-toluamide Following Dermal Application to Human Volunteers DACO 5.8, 10.3.2
3683205	Anthony W. Smallwood et al., 1992, Journal of Analytical Toxicology, Vol. 16, January/February 1992, N,N'Diethyl-m-Toluamide(m-DET): Analysis of an Insect Repellent in Human Urine and Serum by High-Performance Liquid Chromatography DACO 5.14
3683214	Wesley G. Taylor and Roy W. Spooner, 1990, J. Agric. Food Chem., Vol. 38, No. 6, 1990, Identification and Gas Chromatographic Determination of Some Carboxylic Acid Metabolites of N,N-Diethyl-m-toluamide in Rat Urine DACO 5.14
3683217	Jia-Ni Tian et al., 2013, Journal of Environmental Health, Volume 76 Number 6, Urinary Metabolites of DEET After Dermal Application on Child and Adult Subjects DACO 4.8, 5.7
3683221	Lih-Ming Yiin et al., 2015, Environ Sci Pollut Res (2015) 22:7062-7070 DOI 10.1007/s11356-014-3915-3, Assessment of dermal absorption of DEET-containing insect repellent and oxybenzone-containing sunscreen using human urinary metabolites DACO 5.7, 5.8
3683220	Anthony Wu et al., 1979, Journal of High Resolution Chromatography &Chromatography Communications, VOL. 2,SEPTEMBER 1979, High Resolution Gas Chromatography/Mass Spectrometric Characterization of Urinary Metabolites of N,N-diethyl-m-toluamide (DEET) in Man DACO 5.14
2409268	U.S. EPA (2012a). Standard Operating Procedures for Residential Pesticide Exposure Assessment. EPA: Washington, DC. Revised October 2012. DACO 12.5.5

Unpublished information

PMRA document number	Reference
3637667	2019, Interpreting DEET Biomonitoring Data in a Risk Assessment Context: Final Report, DACO: 5.7

E. Information considered in the updated environmental assessment

Additional information considered

Published information

PMRA document number	Reference
795831	MSDS sheet for N,N-diethyl-m-toluamide DACO 8.4.1
3667976	Ambrose, A.M., 1959. Pharmacologie and toxicologic studies on N,N-diethyltoluamide. I. N,N-diethyl-m-toluamide. Toxicol Appl Pharmacol 1:97-115 – Taken from DHHS, 2017. DACO 8.6
3667982	Aronson D, Weeks J, Meylan B, Guiney PD, Howard PH. 2011. Environmental release, environmental concentrations and ecological risk of N,N-diethyl-m-toluamide (DEET). Integrated Environmental Assessment and Management 8(1):135-166. DACO 8.6
3667983	ATSDR, 2017. Toxicological profile for DEET (N,N-diethyl-meta-toluamide). US Department of Health and Human Services: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/toxprofiles/tp185.pdf . DACO 8.6
3667986	Brooke, L.T., D.J. Call, D.L. Geiger, and C.E. Northcott, 1984. Acute toxicities of organic chemicals to fathead minnow (Pimephales promelas), VI. Center for Lake Superior Environmental Studies, University of Wisconsin-Superior. DACO 9.5.2.3
3667987	Carpenter, C.P., C.S. Weil, and H.F. Smyth, 1974. Range-finding toxicity data: List VIII. Toxicol Appl Pharmacol 28:313-319 – Taken from DHHS, 2017. DACO 9.9
3667988	Costanzo SD, Watkinson AJ, Murby EJ, Kolpin DW, Sandstrom MW. 2007. Is there a risk associated with the insect repellent DEET (N,N-diethyl-m-toluamide) commonly found in aquatic environments? Sci. Total Environ 384(1-3): 214-220. DACO 9.9
2937037	de Solla SR, Gilroy ÈAM, Klinck JS, King LE, McInnis R, Struger J, Backus SM, Gillis PL. 2016. Bioaccumulation of pharmaceuticals and personal care products in the unionid mussel *Lasmigona costata* in a river receiving wastewater effluent. Chemosphere. 146: 486-496. DACO 9.5.6
2937191	Supplemental information for: de Solla SR, Gilroy ÈAM, Klinck JS, King LE, McInnis R, Struger J, Backus SM, Gillis PL. 2016. Bioaccumulation of pharmaceuticals and personal care products in the unionid mussel *Lasmigona costata* in a river receiving wastewater effluent. Chemosphere. 146: 486-496. DACO 9.5.6
3667989	ECHA, 2016. N,N-diethyl-meta-toluamide (DEET). CLH Report: Proposal for Harmonised Classification and Labelling. EC Number: 205-149-7. https://echa.europa.eu/documents/10162/7c8cf21e-8bdc-d039-7e75-152a0720f2e5. DACO 12.5.4

PMRA document number	Reference
3667996	McCain W.C., R. Lee, M.S. Johnson, J.E. Whaley, J.W. Ferguson, P. Beall & G. Leach, 1997. Acute oral toxicity study of pyridostigmine bromide, permethrin, and DEET in the laboratory rate. J Toxicol Enviorn Health 50(2):113-124. DACO 9.7
3749327	Mayer, FLJ and MR Ellersieck, 1986. Manual of acute toxicity: interpretation and data base for 410 chemicals and 66 species of freshwater animals. US Department of the Interior, Fish and Wildlife Services. Publication no. 160 DACO 9.9
3667997	Michael AG and GS Grant, 1974. Toxicity of the repellent DEET 9N,N-Diethyl-Metatoluamide) to *Gambusia affinis*. Mosq News. Issue 34, pages 32-35 IN Costanzo et al, 2007. DACO 9.5.2.3
3667998	Seo J., Y.G. Lee, S.D. Kim, C.J. Cha, J.H. Ahn, & H.G. Hur, 2005. Biodegradation of the insecticide N,N-diethyl-m-tolumide by fungi: Indentification and toxicity of metabolites. Arch Environ Contam Toxicol 48(3):323-328. DACO 8.6
3667999	U.S. Army, 1980. Inhalation toxicities of N,N-diethyl-meta-toluamide (M-DET) Study No. 75-51-0034-80, January – May 1979. Fort Sam Houston, TX: U.S. Army – Taken from DHHS, 2017 (MRID 00134359). DACO 4.2.3,4.3.6
3668000	US EPA, 2014. DEET (N,N-Diethyl-meta-tolumaide) : Interim Registration Review Decision. Case Number 0002. EPA-HQ-OPP-2012-0162-0012. DACO 12.5
3668001	US EPA, 2012. Registration review – Ecological risk, environmental fate, and endangered species assessment for N,H-Diethyl-meta-toluamide 9DEET) EPA-HQ-OPP-2012-0162-0002. DACO 12.5
3668003	US EPA, 1998. Reregistration eligibility decision (RED): DEET. Washington, DC. DACO 12.5
3668005	Von Elert E, Preuss K, Fink P. 2016. Infodisruption of inducible anti-predator defenses through commercial insect repellents? Environmental Pollution 210:18-26. DACO 9.9
3668006	Weeks, J., P. Guiney, & A. Nikiforov, 2010. Assessment of the environmental fate and ecotoxicity of N,N-diethyl-m-toluamide (DEET). Integrated environmental assessment and management 8 (1), p.118-132. DACO 8.6, 9.9
3668008	WHO 1987. Data sheet on pesticides No. 80: DEET. World Health Organization. DACO 12.5

Unpublished information

PMRA document number	Reference
2937040	2018. DEET in water and mussels from the Grand River, 2009-2012. DACO 9.5.6
2937053	2018. Supplemental information: DEET in water from Cootes Paradise, Hamilton, Ontario, 2014-2016. DACO 9.5.6
2937184	2018. DEET in water and mussels from the Grand River, 2009-2012. Supplemental information for PMRA No. 2937040 DACO 9.5.6