Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Re-evaluation Decision Document RRD2002-01

Personal insect repellents containing DEET (N,N-diethyl-m-toluamide and related compounds)

The purpose of this Re-evaluation Decision Document is to notify registrants, pesticide regulatory officials and the Canadian public that the re-evaluation of the personal insect repellent DEET is now complete, to describe the reviews undertaken during the course of the re-evaluation and to present the regulatory decisions resulting from the re-evaluation.

(publié aussi en français)

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Decision

This publication documents the conclusions of the Pest Management Regulatory Agency's re-evaluation of personal insect repellents containing DEET. The following is a brief summary of how the re-evaluation decisions apply to the safe use of DEET as an insect repellent for adults and children.

Children:

Children under 6 months of age

- DO NOT use personal insect repellents containing DEET on infants. (Advice unchanged)

Children aged 6 months to 2 years

- **In situations where a high risk of complications from insect bites exist, the use of one application per day of DEET may be considered for this age group**.
- **The least concentrated product (10% DEET or less) should be used. (New advice.)**
- The product should be applied sparingly and not be applied to the face and hands.
- Prolonged use should be avoided.

Children between 2-12 years of age

- **The least concentrated product (10% DEET or less) should be used.**
- **Do not apply more than three times per day. (New advice)** Do not apply to the face and hands.
- Prolonged use should be avoided.

Adults and Individuals 12 Years of Age or Older:

- **Products containing DEET at concentrations above 30% will no longer be acceptable for registration, based on a human health risk assessment that considered daily application of DEET over a prolonged period of time. Studies show that products with lower concentrations of DEET are as effective as the high concentration products, but they remain so for shorter periods of time. Products containing no more than a 30% concentration of DEET will provide adults with sufficient protection. (New advice)**

Table of Contents

1.0 Information used in re-evaluation

Registrants, pesticide regulatory officials and other interested parties were notified in June 1990 through Announcement Document A90-01, *Re-evaluation of Personal Insect Repellents*, of the Pesticides Directorate, Agriculture Canada, that such repellents would be re-evaluated under Section 19 of the Pest Control Products Regulations. The registrants of personal insect repellent products were asked to submit, within 6 months, indices to all known toxicology and efficacy studies on their products, plus copies for re-evaluation of any of the studies that had not already been submitted.

Eight active ingredients were named in the announcement, but only one of them will be considered in this report: DEET (*N*,*N*-diethyl-*m*-toluamide, diethyl toluamide or DTU). Separate documents have been issued on MGK Repellent 326 (di-*n*-propyl isocinchomeronate, or MGD), and MGK Synergist 264 (*n*-octyl bicycloheptene dicarboximide, or MGK) in personal insect repellents[1]. (The other uses of MGK Repellent 326 and MGK Synergist 264 in insecticide products are not under re-evaluation.) Of the five other active ingredients named in the announcement, three (citronyl, dimethyl phthalate and ethyl hexanediol) are no longer registered. The other two (oil of citronella and oil of lavender) are still used in registered personal repellents, but will be re-evaluated separately.

Additional data relevant to the health risk assessment were submitted by the DEET Issues Task Force (DITF) during the course of the re-evaluation. For the re-evaluation of efficacy and value, data submitted by the registrants were supplemented by unpublished reports from other bodies (e.g., Department of National Defence, universities), a survey of the literature up to 1995 and some later publications. Few of the uses of registered products were supported by original efficacy data supplied by the registrants. Even fewer products had data to show efficacy against groups of pests, other than mosquitoes and blackflies, and no product-specific efficacy data at all were found for some groups such as fleas and chigger mites.

The companies comprising the DITF and DEET Joint Venture asked that it be noted in this Re-evaluation Decision Document that they do not agree with some of the observations, analyses and conclusions that it contains.

2.0 Regulatory history

Personal insect repellents containing DEET have been registered in Canada since 1957. As of July 6, 2001 there were 127 registered end-use products (EPs) containing DEET, all personal insect repellents, from 41 registrants. Four of the products contained DEET in

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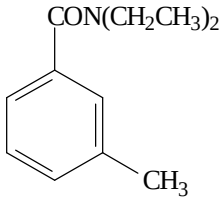
[1] see RRD2001-01, *Di-n-propyl isocinchomeronate (MGK Repellent 326)* and RRD2001-02, *n-Octyl bicycloheptene dicarboximide (MGK Synergist 264*)

combination with MGK Synergist 264, and 13 contained DEET in combination with both MGK Repellent 326 and MGK Synergist 264.

3.0 The active substance, its properties, uses, proposed classification and labelling

3.1 Identity of the active substance

Function	Insect repellent
Chemical names: International Union of Pure and Applied Chemistry Chemical Abstracts Service (CAS)	 *N*,*N*-diethyl-*m*-toluamide *N*,*N*-diethyl-3-methylbenzamide
CAS No.	134-62-3
Molecular formula	$C_{12}H_{17}NO$
Molecular weight	191.26
Structural formula	
Identity of relevant impurities of toxicological, environmental or other significance	Based on an evaluation of the beginning materials and the manufacturing process used, the Technical Grade Active Ingredient (TGAI) is not expected to contain toxic microcontaminants known to be Track-1 substances under the Toxic Substances Management Policy.

Registration numbers, purity and basic manufacturers		
Reg. No.	Purity of the TGAI	Basic manufacturer
18068	97.5% (nominal)	Morflex, Inc.
18091	97.5% (nominal)	McLaughlin Gormley King Co.
23785	95% (minimum)	Clariant Corporation

3.2 Identity of formulants in EPs

The specification forms on the files for EPs containing 7.5–75% DEET registered as of February 2000 were reviewed. (EPs with guarantees of 95–100% DEET were not included in the survey, because they have no formulants.)

Many of the specification forms were old, and most of them did not include the CAS numbers for formulants, which are now required.

Conclusion

New specification forms that meet the requirements stated in Regulatory Directive DIR98-03, *Chemistry Requirements for the Registration of a Manufacturing Concentrate or an End-Use Product*, will be required for all DEET EPs that meet the criteria for continued registration. Formulants will be subject to the criteria that will be outlined in the new formulants policy, the basics of which were published in Regulatory Proposal PRO2000-04, *Formulants Policy,* when it is implemented.

3.3 Methods of analysis

3.3.1 Methods for analysis of the active substance as manufactured

Studies to determine the active ingredient and the significant structurally related impurities (content ≥ 0.1%) in the TGAI were submitted.

3.3.2 Method for formulation analysis

The analytical method for the determination of the active ingredient in the EPs was provided.

4.0 Classification and labelling of products

Two sources of technical DEET were registered (Reg. Nos. 18068 and 18091 for one source, Reg. No. 23785 for the other). There were two manufacturing intermediates containing DEET, MGK Repellent 326[2] and MGK Synergist 264[2] (Reg. Nos. 19647 and 21830), and one intermediate containing DEET and MGK Synergist 264 (Reg. No. 21984).

Of the 127 EPs containing DEET that were fully registered as of July 6, 2001, the most common formulations were pressurized sprays (37% of the products) and solutions, including undiluted liquids and pump sprays (also 37%). The water-based emulsions

[2] As a part of the re-evaluation of personal insect repellents the manufacturer of MGK 264 and MGK 326 has agreed to voluntarily discontinue sale of these active ingredients for use in personal insect repellents.

(22%), usually sold as creams or lotions, included three “extended duration” products, a term used for microencapsulated, microparticulate, polymer or any other formulations designed to extend the residual action of the repellent. The four products classified as “impregnated fabrics” were all towelettes (tissues impregnated with DEET solutions). There was also one paste product containing DEET. Although 72% of the EPs contained 30% or less of technical DEET, 9% of the products consisted of undiluted technical DEET (shown as 95% DEET on some labels and 100% on others). There were 13 EPs that contained sunscreen compounds as well as DEET.

The English text of the labels of all the DEET EPs (as of July 6, 2001) includes the claim that they repel mosquitoes, and nearly all of them are claimed to repel black flies. Many of them are also claimed to repel fleas, ticks, stable flies and chiggers (Table 1). The identity of these taxa is generally agreed and understood. The labels of some products, however, have claims that are either too general (e.g., ‘biting flies,’ ‘flies’) or ambiguous (e.g., ‘gnats,’ ‘sand flies,’ ‘midges’). An earlier survey of pest names in the French text of labels revealed that, for many products, the names used were also vague or ambiguous (Table 1).

In a 1999 survey of the label text of DEET EPs, precise dosage instructions (e.g., “apply 6–8/8–10 drops,” “impregnate with amount of repellent recommended”) were found on only 3% of the labels. Most other products had imprecise instructions (e.g., “Apply a thin layer,” “Spray clothing and exposed skin”). The labels of 22% of the products had precise claims of how long their protection would last, ranging from 1 to 8 h against mosquitoes for repellents applied to the skin. The labels of another 20% of the products had vaguer claims (e.g., “lasts for hours”), 19% said “repeat application as required” and 36%, the largest group, had no claims as to the duration of protection. Thus, the labels of many registered products had no precise dosage instructions, nor any protection time claims with which the available efficacy data could be compared.

Table 1 Numbers of repellent products registered (as of July 6, 2001) by active ingredient, and groups of pests against which repellency is claimed in the English text of labels. (Numbers in each column should not be added together, because most products claim repellency against more than one group of pests.)

Pest name in English label text (2000)**	Active code*			Total pests	Percent of total	Equivalent names in French text of labels (1996 survey)**
	DTU	DTU + MGD + MGK	DTU + MGK			
Mosquitoes	110	13	4	127	100	**Moustiques, Maringouins**
Gnats	32	5	2	39	30.7	Cousins, Thrips
Black Flies	103	8	4	115	90.6	**Mouches noires, Simulies**
Biting Midges	17	4	2	23	18.1	**Brûlots**
Sand Flies	22	1	1	24	18.9	Phlebotomes, Mouches des sables
Midges	4	0	0	4	3.1	Moucherons, Frelons
Deer Flies	8	0	1	9	7.1	**Mouches à chevreuil, Chrysops**, Taons
Stable Flies	27	3	1	31	24.4	**Mouches piquantes des étables**
Biting Flies	5	1	0	6	4.7	Mouches piquantes
Flies	3	0	0	3	2.3	Mouches
Fleas	56	7	4	67	52.8	**Puces**
Biting Insects	1	0	0	1	0.8	Insectes piquants
Insects	2	0	1	3	2.4	Insectes
Chiggers	35	2	1	38	29.9	**Aoûtats, Rougets,** Chiques, Mites
Ticks	68	8	3	79	62.2	**Tiques**
American Dog Tick	1	0	0	1	0.8	**Tique américaine du chien**
Brown Dog Tick	1	0	0	1	0.8	**Tique sanguine,** Tique brune du chien
Total products	110	13	4	127	—	
% of total	86.6	10.2	3.1	99.9	—	

* DTU, *N*,*N*-diethyl-*m*-toluamide (DEET); MGD, di-*N*-propyl isocinchomeronate (MGK Repellent 326); MGK, *n*-octyl bicycloheptene dicarboximide (MGK Synergist 264).

** Currently acceptable English and French common names for bloodsucking Arthropods that occur in Canada are shown in **bold**. Names not shown in bold will no longer be acceptable on the labels of personal insect repellents because they are too general (e.g., gnats, biting flies, biting insects) or mistranslated (e.g., chiques, frelons, mites, thrips) or because the arthropods named are not pests in Canada (e.g., sand flies) or do not feed on blood at all (e.g., midges).

5.0 Effects having relevance to human health

5.1 Toxicology and metabolism

In rats, DEET was rapidly and extensively absorbed and widely distributed into all tissues following oral dose administration. Absorption was much slower after dermal dosing; blood levels of total radioactivity during the first 24 h post-dosing and tissue levels of total radioactivity at the time of peak blood levels were more than an order of magnitude lower following dermal dose administration than those seen following a comparable oral dose. At the time of peak blood concentrations, the highest non-dose site tissue concentrations occurred in the kidneys, regardless of the route of administration. DEET was rapidly eliminated, primarily in the urine. Elimination in the feces ranged from 3 to 7% of the administered dose and no appreciable amount of DEET was expired in air as volatiles. DEET did not bioaccumulate in tissues. DEET was fully metabolized, with two major urinary metabolites identified as an oxidized derivative of DEET as well as an oxidized and dealkylated derivative. No significant differences in absorption, distribution, metabolism or excretion were evident between males and females following oral or dermal administration. The rate of elimination was increased in rats that received multiple oral doses of DEET, suggesting that DEET induced the liver microsomal enzyme system.

In laboratory animals, DEET was of low acute toxicity via the oral, dermal and inhalation routes of exposure. The lowest acutely lethal oral dose was 750 mg/kg in the pregnant female rat in a developmental toxicity study. Based on a comparison of acute doses that result in 50% mortality, females appeared slightly more sensitive than males and young animals appeared more sensitive to high acute oral exposures than adults. Clinical signs of toxicity at near lethal doses included ataxia, tremors, prostration, lack of balance, convulsions, chromodacryorrhea (rat), lethargy (rat, rabbit) and hind limb extension (rabbit). DEET was a moderate but reversible eye irritant, and a slight dermal irritant in rabbits. While DEET did not elicit skin sensitization reactions in guinea pigs, there are indications that, in rare cases, allergic skin reactions may develop in humans.

In both short- and long-term repeat-dosing toxicity studies, the most common treatment-related effects were reduced body-weight gain and food consumption and liver and kidney effects. Reduced body-weight gain was the most sensitive indicator of toxicity regardless of the species and route of exposure (oral or dermal). Rats and hamsters were comparably sensitive to DEET following short-term dietary exposure. The lowest observed adverse effect levels ranged from 300 to 500 mg/kg bw/d based on reduced terminal body weights ($\leq$10%). Long-term exposure in rats, mice and dogs did not significantly increase toxicity. Mice appear to be less sensitive to the effects of DEET than rats. DEET was not found to be mutagenic, nor was it carcinogenic in either rats or mice.

In male rats, kidney lesions, including hyaline droplet formation and granular cast accumulation in the renal tubules, chronic inflammation and tubular epithelial regeneration, were often noted following subchronic oral and dermal dosing. This renal pathology was shown to be associated with an accumulation of $\alpha_{2\mu}$-globulin accumulation

in renal tubules that occurs uniquely in male rats. Since humans do not produce $\alpha_{2\mu}$-globulin, this syndrome of kidney lesions is not considered relevant to humans; therefore, these findings were not considered in the setting of no observed adverse effect levels (NOAELs) in the toxicity studies.

Kidney weights were also variably affected in rats, mice and micropigs; this was associated with possible kidney pathology only at high doses in female rats following subchronic dermal dosing. Increased liver weights following subchronic or chronic dosing regimens in rats, mice and micropigs were considered a nonadverse, adaptive response and were not considered in the setting of the NOAELs. Other findings for which the incidence was higher than the controls in mice at high doses included lymphoid hyperplasia of the spleen and mesenteric lymph node and inflammation of the salivary gland and urinary bladder after chronic exposure.

No adverse reproductive toxicity was observed in rats over two generations, although in hamsters, testes and epididymides weights were reduced, with testicular tubular degeneration and cellular debris in the lumen of the epididymides noted after subchronic exposure. In the two-generation reproductive toxicity study, parental toxicity (reduced body-weight gain and food consumption) was observed in the high dose males and females in the second (F_1) generation only. Effects in young rats were restricted to reductions in body-weight gain in both generations (F_1 and F_2) of pups; this effect occurred in the high dose group only during the lactation period when maternal intake of DEET was increased up to twice the premating dose level.

No teratogenicity or age-related sensitivity was observed in either rat or rabbit developmental studies. Minor developmental effects were observed in both rats (decreased fetal body weights and delayed ossification) and rabbits (delayed ossification), but only at maternally toxic dose levels. In rats, maternal toxicity included mortality, clinical signs of toxicity and reduced body-weight gain. In rabbits, maternal toxicity included reduced body-weight gain and food consumption. Although the acute lethality studies suggested an age-related sensitivity at high doses, no evidence for such a sensitivity was seen in the remainder of the database.

While DEET was not a selective neurotoxicant in rats, effects on a few functional observational behavioural parameters were noted in neurotoxicity studies. Acute exposure at 500 mg/kg bw resulted in decreased motor activity, tremors, increased vocalizations, piloerection and slowed reaction to induced pain either 1 or 24 h after exposure or both. No neuropathology was observed at nonlethal doses. Chronic exposure to second generation rats selected from the reproductive toxicity study resulted in increased motor activity only at systemically toxic doses.

As with other common household products, many DEET-related calls to Poison Control Centres involved young children less than 6 years of age who had accidentally ingested DEET products. This is likely indicative of product accessibility rather than increased susceptibility to toxicity. Incidence data for all age groups, including cases of oral

ingestion by young children, showed that most poisoning incidents were asymptomatic or of minor significance. Those incidents resulting from a dermal exposure usually involved eye or skin irritation. Although rare, neurotoxic symptoms have occurred in humans and include nausea, vomiting, headache, lethargy, weakness, seizures, tremors, numbness, dizziness and fainting; the few fatal cases, including those that involved children, generally followed excessive or repeated exposure. This data did not clearly identify product concentrations of concern. Given the extensive use of DEET, the reports of adverse outcomes associated with DEET are infrequent. Proposed regulatory limitations and label improvement recommendations will help to ensure that adverse outcomes following the use of DEET will be even less frequent.

5.2 Consumer exposure and risk assessment

For all populations, two exposure scenarios were identified: acute (occasional use) and intermediate (prolonged use) dermal exposure. For toddlers aged 6 months to 2 years, one additional exposure scenario was identified: nondietary oral exposure resulting from the transfer of residues from the skin to the mouth during hand-to-mouth activities. Significant exposure from the inhalation route was not anticipated for any population. Since age-related susceptibility was not regarded as a significant concern for DEET, the toxicological end points used in the acute and intermediate-term dermal risk assessments were considered to be applicable to all populations, including children aged 6 months through 12 years.

For the acute dermal risk assessment, no appropriate acute dermal study that adequately assessed neurotoxic parameters was available. The most sensitive indicator of toxicity following an acute oral exposure was seen in the neurotoxicity study in rats following a single oral dose. The NOAEL in this study was 200 mg/kg bw and was based on behavioural and clinical observations at 500 mg/kg bw in males and females at 1 and 24 h post-dosing. A standard 100-fold margin of exposure (MOE) is required; this accounts for extrapolation between species (10-fold) and variability within the human population (10-fold).

For the intermediate-term dermal risk assessment, the most relevant toxicity end point was the NOAEL of 300 mg/kg bw/d from the 90-d rat dermal toxicity study, based on decreased body-weight gain in males and marginal renal pathology in females at 1000 mg/kg bw/d. This end point was selected because it represents the most sensitive indicator of toxicity following repeated dosing and was derived from a study that used the dermal route of exposure. The standard 100-fold MOE is required for this end point.

For the acute incidental (nondietary) oral exposure in children aged 6 months to 2 years, the end point and MOE used for the above acute dermal risk assessment was also considered the most appropriate end point, since it was derived from an acute study using the relevant route of exposure (oral) and assessed the most sensitive acute end point (neurotoxicity). Again, since children are not considered to be more sensitive to the effects

of DEET, no additional uncertainty or safety factors above and beyond the standard 100-fold MOE were warranted in risk assessment.

5.2.1 Consumer exposure

Consumer exposure potential was estimated using survey data and a usage study. The usage study involved over 540 subjects including men, women and children and took place in three locations in the U.S. (Wisconsin, Oregon, Florida). The weight of the product container was recorded pre and post application, with the difference providing an estimate of the amount of product used per application. There was not a significant difference between population groups (e.g., men vs. women vs. children) in the amount of product applied during a single use. Differences were, however, noted in the amount of product applied depending on product type. Aerosols were found to be the most frequently selected and also resulted in the highest amount of product applied. The estimated average amount of product applied (3.7 g product/person per application), however, was based on all formulation types. An exception to this was made for products with 100% DEET, as the majority of these products are either pumps or liquids. In these cases, the estimated average amount of product applied was 2.3 g product/person per application.

Dermal exposure estimates for adults and children were calculated for typical use (one application per day) or high-end use (2–3 applications per day depending on protection time and assuming 12 h of protection would be needed). The timing of reapplication was based on the protection time attributed to a given concentration of DEET (e.g., a 50% DEET product has an average protection time of 7.5 h; therefore, it was assumed the product would be reapplied after 7.5 h). The default body weights used in the assessment were 70 kg for the average adult (male and female) and 27 kg for children 2–12 years of age.

The assessment of exposure to toddlers (children aged 6 months to 2 years) quantified dermal exposure and incidental nondietary ingestion (resulting from hand-to-mouth contact). For dermal exposure, there were no population-specific use data for toddlers. Therefore, the total amount of DEET applied (grams product per person per application) was assumed to be the same as that calculated for adults and children. As the body surface areas for toddlers are significantly lower than those of adults and children aged 2–12, this estimate of total product applied is considered to be conservative. As in the adult and child assessment, toddler exposure estimates were calculated for typical use (one application per day) or a high-end use (2–3 applications per day depending on protection time and assuming 12 h of protection is needed). A default body weight of 10.2 kg was used for children 6 months to 2 years of age using the average values for male and female children.

Toddlers (6 months to 2 years) could also be exposed to DEET via the oral route through hand-to-mouth contact. Although the proposed label instructions prohibit direct application to the hands of toddlers, it was assumed that DEET from treated areas of skin could be transferred to the hands and subsequently ingested through hand-to-mouth activities. A method to quantify exposure from this pathway was derived using some of

the principles of the 1997 U.S. Environmental Protection Agency (EPA) draft *Standard Operating Procedures for Residential Exposure Assessment*. This assumed that 1 mg/cm^2 of product was present on the skin over a given area and that 100% of the DEET is transferred to the hands upon contact (i.e., hands would then have 1 mg/cm^2 product). It is then assumed that each oral exposure event involves the child placing the palmar surface of three fingers of one hand (20 cm^2 surface area) into their mouth. A saliva extraction factor of 0.5 (50%) was applied to determine the quantity of product extracted from the hand. The total oral ingestion resulting from single or multiple hand-to-mouth events was then calculated.

Combination sunscreen and DEET products were assessed separately. As sunscreens require frequent and liberal application, combination sunscreen and DEET products would be applied in a manner inconsistent with other DEET products. In the exposure assessment of these products, an application rate for sunscreens of 2 mg product/cm^2 was assumed to be applied to exposed skin (upper and lower arms, upper and lower legs, hands and face), where the area of exposed skin was estimated to be 10 000 cm^2 for adults and 5 000 cm^2 for children. This results in total exposure estimates of 20 g product/adult per application and 10 g product/child per application.

5.2.2 Acute dermal risk assessment

In a standard risk assessment, exposure estimates are compared directly to the toxicological end points to derive an MOE. In the case of DEET, however, due to the high exposure estimates resulting from the mode of use (i.e., direct application to skin), a novel approach was used to refine the risk assessment. The acute oral NOAEL was converted to a dermal equivalent NOAEL by comparing pharmacokinetic data from rats following oral and dermal dosing. Several studies were available that measured DEET (and in some cases also its metabolites) in plasma following oral and dermal dosing.

In one set of studies, levels of radioactivity were quantified in blood for 24 h following oral and dermal dosing at 100 mg/kg bw with ^{14}C-DEET. For oral dosing, sex-related differences were seen in the time to peak blood levels of radioactivity (30 min in males and 2 h in females) and the mean peak blood levels of radioactivity (40.2 µg DEET equivalents/mL for males and 27.2 µg DEET equivalents/mL for females). After dermal dosing, no definitive peaks in DEET blood level were observed in either the male or female rats. The mean peak blood levels following dermal dosing were estimated to be 1.8 µg DEET equivalents/mL in males and 1.4 µg DEET equivalents/mL in females. The time to peak was difficult to ascertain, however, it was estimated to be approximately 2 h in males (the blood value at this time was similar to mean blood values from hours 1 to 4) and 3 h in females (the mean peak blood value was similar to values between 1 and 6 h).

Two other rat studies that quantified only parent DEET in plasma following a single oral dose of 200 mg/kg bw DEET demonstrated opposite sex-related trends for DEET in plasma (i.e., females demonstrated higher peaks than males). The results from one of the studies were extremely variable, which was possibly attributed to improper dose administration, and were therefore not given further consideration. In the second study, the mean peak plasma levels occurred at 0.5 h in both males and females; the mean peak values at this time were 7.1 µg/mL for males and 15.2 µg/mL for females. Complete elimination of parent DEET from plasma occurred between 12 and 24 h.

Another study examined parent DEET in plasma in rats following a single or five consecutive daily dermal doses of 1000 mg/kg bw. The application site remained uncovered and was not washed or wiped off between applications. As in the previous two oral dose rat studies, the female plasma values were consistently higher than the male plasma values following single and consecutive doses. Following a single dose, the peak plasma level in males was 5.6 µg/mL, 4 h post-dosing; in females, it was 26.6 µg/mL, 8 h post-dosing. Following five consecutive daily doses, the time to mean peak values was 8 h for both males and females; the mean peak values were 4.8 µg/mL in males and 17.4 µg/mL in females.

DEET concentrations in plasma following oral or dermal dosing were also examined in other species. Gelatin capsules of DEET (75 mg/kg bw/d) were administered to Beagle dogs for 4 consecutive days. Unlike the rat, there were no sex-related differences in peak plasma levels. On day 1, the highest mean plasma level was 18.3 µg/mL for males, whereas the highest mean plasma level for females was 14.0 µg/mL. Repeated oral administration over 4 days did not result in significantly different plasma levels in either the male or female dogs, with mean peak plasma levels reported as 14.2 µg/mL for males and 12.5 µg/mL for females. Parent DEET was eliminated from the plasma by 6 h.

Plasma levels of DEET were also monitored in human volunteers following dermal application using a single application as well as after 4 consecutive days of applications. Approximately 3 g (62 mg/kg bw/d) of undiluted DEET was applied topically to three females and 4 g (57 mg/kg bw/d) was applied to three males once a day for 4 consecutive days. The application areas included one arm and both legs. The application sites were left uncovered for 8 h, after which time the treatment site was washed with soap and water. DEET plasma levels increased gradually during the exposure period and reached a maximum immediately before or shortly after showering, with time to peak plasma levels generally being reported as 8–9 h. The mean peak plasma values on day 1 were 0.43 µg/mL for females and 0.62 µg/mL for males. A similar trend of slightly higher male plasma levels was noted in the day 4 values as well, with the mean peak plasma levels being reported as 0.25 µg/mL for females and 0.49 µg/mL for males. This sex difference is opposite to what was noted in all of the rat DEET plasma level studies (i.e., those studies that measured parent DEET rather than total radioactivity). The DEET plasma concentrations were below the limit of quantification within 24 h after application.

Since exposure is primarily dermal and the acute risk assessment is based on an acute oral NOAEL obtained from a rat toxicity study, peak plasma or blood levels in the rat following oral and dermal dosing were compared to derive an oral to dermal conversion factor. There was considerable variability, however, in potential conversion factors that could be derived depending on the data selected. Based on the study examining radiolabelled DEET at equivalent oral and dermal dose levels, ratios ranging from 19 for males (27.2 vs. 1.4 µg/mL) to 22 for females (40.2 vs. 1.8 µg/mL) were derived. The other studies that measured only parent DEET in plasma did not use equivalent dosing levels; therefore, the plasma values were corrected to account for this difference, assuming plasma concentration changes linearly with dose. In these studies, the resulting oral to dermal peak plasma ratios were 2.9 for females (15.2 vs. 5.3 µg/mL) and 6.4 for males (7.1 vs. 1.1 µg/mL). Given some of the inconsistencies in the rat blood level studies (e.g., sex differences appeared in some studies, but not in others; the unknown nature of the radioactivity measured in one study), a conservative approach using the lower ratios developed on the basis of measured levels of parent DEET was considered the most appropriate. Pooling the male and female ratios resulted in a final conversion factor of approximately 5. This value is multiplied by the NOAEL of the acute oral neurotoxicity study to derive a dermal equivalent in the acute risk assessment.

In addition to the conversion of the acute oral NOAEL to a dermal equivalent, a further refinement to the risk assessment was incorporated. Numerous studies estimating the dermal absorption of DEET in humans and rats have demonstrated that there is approximately a 5-fold difference in DEET dermal absorption in rats (38.5% on average) and humans (7.5% on average). This 5-fold correction was factored into both the acute and intermediate risk assessment.

Based on the two factors, the acute dermal MOE was calculated using the following equation:

$$\text{Acute MOE} = \frac{\text{Acute oral NOAEL} \times \text{5 (rat oral-to-dermal conversion factor)} \times \text{5 (rat-to-human dermal absorption correction factor)}}{\text{human dermal exposure}}$$

Using this approach and the dermal exposure levels calculated for adults and children, the acute risk assessment resulted in acceptable MOEs for adults for all concentrations of DEET products for both single and multiple applications per day. For children, acceptable MOEs were obtained for products up to 35% DEET for a single application per day. For multiple applications per day, however, only products up to 10% DEET were acceptable.

Acute risk assessments were also performed for combination DEET+sunscreen products for adults and children. Unacceptable MOEs were obtained for these products for both adults and children using multiple applications per day.

The toddler risk assessment was considered separately from the adult and child risk assessment. This assessment requires the combination of exposure from two routes: dermal and oral (nondietary ingestion associated with hand-to-mouth contact). The dermal risk assessment is performed in the same manner as for adults and children (i.e., the oral NOAEL of 200 mg/kg bw/d is transformed to a dermal equivalent by multiplying it by 5 and corrected for differences in rat and human dermal absorption by multiplying it again by 5). For the risk assessment of the nondietary route of exposure, however, the NOAEL derived from the acute neurotoxicity study may be used directly with the estimated oral exposure to calculate an MOE (i.e., no route-to-route extrapolation is necessary, as the oral route that was used in the study is representative of the route of exposure). In quantitative risk assessments, the risks associated with separate routes of exposure are combined if the toxicological end point is common to both routes of exposure. In the case of the toddler risk assessment for DEET, the risks associated with the dermal route of exposure are combined with that associated with the oral route (hand-to-mouth) of exposure, as the toxicological end point for each route is the same. The risks are combined using the following equation (where MOE_T is the margin of exposure for toddlers):

$$MOE_T = \frac{1}{\frac{1}{MOE_{Oral}} + \frac{1}{MOE_{Dermal}}}$$

Combined MOEs were calculated for all concentrations of formulation and for single and multiple (within a day) dermal application scenarios. Based on a single application per day, adequate MOEs are achieved for approximately 6–8 hand-to-mouth events for products containing up to 10% DEET. When products with concentrations of 15% or greater are examined, inadequate MOEs are obtained based only on the dermal assessment (i.e., not considering any hand-to-mouth events). When multiple dermal applications within a day are considered, inadequate MOEs are obtained for all concentrations.

5.2.3 Intermediate risk assessment

DEET may also be used on a daily basis for a prolonged period. The MOEs for intermediate dermal exposure for various DEET products for children and adults were calculated using the 90-d dermal rat NOAEL of 300 mg/kg bw/d and correcting for the difference in dermal absorption between rats and humans using the dermal absorption correction factor of 5. The intermediate MOE was calculated using the following equation:

$$\text{Intermediate MOE} = \frac{\text{intermediate dermal NOAEL} \times 5 \text{ (rat-to-human dermal absorption correction factor)}}{\text{human dermal exposure}}$$

Based on this approach, acceptable MOEs are only obtained for adults with products having concentrations of 30% DEET and less. For children, acceptable MOEs are only obtained for products containing 10% or less DEET. Inadequate MOEs were obtained for combination DEET+sunscreen products for both adults and children. For toddlers, inadequate intermediate-term MOEs were obtained for all concentrations of DEET products.

5.3 Conclusions

Based on the MOEs for this risk assessment, some restrictions on DEET products are required. Products with greater than 30% DEET resulted in inadequate intermediate-term MOEs for adults and, as such, products should be restricted to concentrations of 30% and less.

For children (2–12 years), acceptable acute and intermediate-term MOEs were only derived for products with up to and including 10% DEET. Based on these results, only products containing 10% DEET or less are acceptable for use on children.

For toddlers, acute MOEs were only acceptable for a single application of products with up to 10% DEET; however, intermediate-term MOEs were inadequate at all concentrations of DEET. As such, all products should carry a statement that reads: “In 6 month to 2 year olds, do not apply more than once a day.”

A risk assessment was not performed for children under 6 months of age, since it is assumed that nonchemical measures can be utilized to protect this population from biting pressures. Consequently, all products should carry the statement: “DO NOT USE on infants less than 6 months of age.”

Based on the human incident data, it is recommended that all labels be standardized with respect to First Aid statements.

As insufficient data were provided to determine exposure to DEET when wearing DEET-impregnated clothing, an MOE cannot be determined. Exposure to these products, however, should not result in a greater potential exposure than products of the same concentration applied directly to the skin. As such, the same recommendations should be applied to these products.

With respect to combination DEET+sunscreen products, required label statements for DEET products vs. sunscreen products present difficulties. The statement “apply liberally/generously” is a label requirement for primary sunburn protectants, whereas the statement “apply sparingly” is a DEET label requirement. The acute MOEs for 10% DEET+sunscreen products are adequate for adults and children based on a single application, however, when multiple applications are considered, MOEs do not reach the target value of 100. The intermediate-term risk assessments results in inadequate MOEs

for DEET and sunscreens containing 10% DEET or more. The combination products should be discontinued.

5.4 Consultations

The draft risk assessment for DEET was provided to the DITF for comment. In a detailed response, the DITF identified several main areas of concern they had regarding the draft risk assessment for DEET. Primarily, the DITF disagreed with the NOAEL established for the 90-d dermal toxicity study used in the intermediate-term risk assessment. They also disagreed with the method used to generate the conversion factor to derive a dermal equivalent NOAEL from the acute neurotoxicity study that was used in the acute dermal risk assessment. Instead they proposed several alternative approaches to performing the acute risk assessment.

In addition to the comments received from the DITF and in light of the complexities of the DEET risk assessments, the PMRA also sought the input of a Scientific Advisory Panel (SAP). The SAP, comprised of five representatives of the Canadian Pediatric Society, was asked to address specific questions relating to the data used in the risk assessments and was also asked to comment on the use of combination products that contain both sunscreen and insect repellent. A Health Canada representative from the Bureau of Pharmaceutical Assessment (BPA), also participated in the consultation process. The outcome of these consultations is summarized below.

The 90-d dermal toxicity study was considered to be the most relevant toxicological end point for the draft intermediate-term risk assessment. The NOAEL for this study was 300 mg/kg bw/d based on decreased body-weight gain in males and mild renal toxicity in females at 1000 mg/kg bw/d. The DITF concluded that the NOAEL for this study should be 1000 mg/kg bw/d based on their views that these effects were not treatment related or were not relevant to humans. Upon consultation, both the SAP and the BPA representative concurred that the study NOAEL should in fact be 300 mg/kg bw/d. This is consistent with the conclusions drawn by other regulatory agencies such as the U.S. EPA and the California Department of Pesticide Regulation. As a result, no change was considered necessary and the critical toxicological end point for the intermediate-term dermal risk assessment continues to be the 90-d dermal toxicity NOAEL of 300 mg/kg bw/d.

In the draft acute dermal risk assessment, the acute oral rat neurotoxicity NOAEL of 200 mg/kg bw/d was converted to an equivalent dermal NOAEL using pharmacokinetic data from the rat.

To do this, the area under the curve, which represents the total absorbed dose over a 24-h period following oral and dermal dosing in a rat pharmacokinetic study, was used as the basis of comparison to derive a conversion factor of 4.5. This was considered appropriate because clinical signs of toxicity were noted in the neurotoxicity study for up to 24 h post-dosing. The DITF discounted the effects at 24 h and concluded that the effects seen in the

neurotoxicity study after 1 h correlated with the peak plasma concentrations (C_{max}) observed in the pharmacokinetic study. Therefore, the DITF proposed an 18-fold conversion factor based on a comparison of C_{max} values. Assuming that there likely is a rapid ingress and egress of DEET from the brain, the SAP agreed that the C_{max} was a better reflection of the observed toxicity and therefore should be used to derive the conversion factor. No specific value or set of data was recommended by the SAP. The representative from the BPA highlighted the variability in the pharmacokinetic data (i.e., no consistency in differences in male and female results, the lack of clear peaks in the plasma concentrations) and indicated that the area under the curve would be a more appropriate basis of comparison. The representative from the BPA further indicated that if the C_{max} was to be used, the 18-fold ratio recommended by the DITF was particularly inappropriate. In light of both these opinions, a more conservative approach than that suggested by the DITF was taken; the resulting 5-fold conversion factor was based on a different set of C_{max} data from the rat pharmacokinetic database.

Although the use of DEET products has, until now, been contraindicated for children under 2 years of age, the rising concern over mosquito-borne illnesses (e.g., West Nile Virus) necessitated that a risk assessment for this population be conducted. Based on the draft assessment, the SAP provided "cautious support for the use of DEET in children between the ages of 6 months and 2 years" and indicated that "there are clearly high risk situations in many parts of Canada related to infant exposure to mosquitos and other insects." The SAP also provided suggested wording for the directions for use for the toddler population that have been incorporated into the label recommendations. It should also be noted that the use of these products on children under 6 months of age was not supported by the SAP.

Historically, combination products containing both sunscreens and insect repellents such as DEET have been registered under the *Pest Control Products Act* (PCPA) and the *Food and Drugs Act*. It was considered possible, that use of these products could lead to an overapplication of DEET due to the discordant use instructions (i.e., sunscreens should be applied liberally and frequently to maximize protection from the sun, but insect repellents such as DEET should be applied only sparingly and infrequently). In light of this, the SAP indicated they do "not believe that there is any clinical justification for the continued listing of combination products containing sunscreen and DEET." This view was also supported by the BPA.

6.0 Value assessment

6.1 Biology of pests

The arthropods named on the labels of registered personal insect repellents are considered pests because they are known or suspected to bite people and feed on blood. In mosquitoes (Culicidae), black flies (Simuliidae), biting midges (no-see-ums, Ceratopogonidae) and deer flies (Tabanidae), only the adult females are blood feeders. In stable flies (*Stomoxys calcitrans*) and fleas (Siphonaptera), adults of both sexes are blood

feeders. In chigger mites (Trombiculidae), it is only the larvae that feed on vertebrate blood, but in ticks (Acarina), both sexes in all mobile stages (larvae, nymphs and adults) are blood feeders. In Canada, people are not the principal sources of blood for any of these pests, and are merely accidental hosts of some of them (e.g., stable flies, cat fleas).

6.2 Medical importance

Blood feeding can cause annoyance, blood loss, allergic reactions or paralysis (rocky mountain wood tick) and may infect people with diseases. Although rare, arthropod-borne diseases known to occur in Canada include viral encephalitis (Western Equine, Eastern Equine and St. Louis), transmitted by *Culex* mosquitoes, and Lyme disease, transmitted by the blacklegged tick (*Ixodes scapularis*). West Nile Virus was first detected in North America in 1999, and was detected in wild birds from southern Ontario by the summer of 2001. The occurrence or threat of these diseases stimulates sales of personal insect repellents in Canada.

The Travel Medicine Program, Laboratory Centre for Disease Control, Health Canada advises travellers abroad to use personal insect repellents to protect themselves against tropical diseases such as malaria, which is transmitted by *Anopheles* mosquitoes (not major pests in Canada), and leishmaniasis, which is transmitted by Phlebotomine sand flies (rare and never pests in Canada). See the malaria prevention web site www.hc-sc.gc.ca/hpb/lcdc/malar97/index.html for an example. Travellers may buy Canadian products for this purpose before departure. Neither the re-evaluation of DEET nor the value assessment for new personal insect repellents submitted for registration have included estimates of their potential value in other countries. While the effectiveness of personal insect repellents containing DEET in protecting people against arthropod-borne diseases is not well documented for any country, it is likely that Canadian DEET products used in other countries would be as effective as any locally purchased equivalents.

6.3 Relative importance of pests

The principal bloodsucking arthropod pests in Canada are *Ochlerotatus* and *Aedes* mosquitoes, especially snowmelt mosquitoes of the *Oc. communis* group in spring and *Ae. vexans* in summer, and black flies, especially members of the *Simulium venustum* complex. Stable flies and deer flies can be very troublesome in some places, and tick bites are feared because of Lyme disease, but mosquito and black fly problems probably account for most of the sales of personal insect repellents in Canada. Many DEET products are also claimed to repel other pests, but it has not been determined whether this is because the other pests are important, or because they were already part of the use pattern for DEET.

6.4 Rationale for reassessment of value

As stated in A90-01, one of the six factors in the decision to re-evaluate personal insect repellents was that "There is some uncertainty that all registered products are efficacious for the pests, uses and protection times claimed." This led to the call for efficacy data, and to the literature survey.

6.5 Data review

6.5.1 Methodology

6.5.1.1 Flying insects

Most of the efficacy data reviewed were gathered by treating the forearms or lower legs of test subjects with standard dosages of the repellent, and exposing the treated areas continuously or intermittently to unfed insects in a cage, or to biting populations in the field. The usual index of efficacy has been the complete protection time (CPT), which is defined as the time from application of the repellent to the first *confirmed* bite (a bite followed by another within 30 min). This is an appropriate index for EPs, because most users want *complete* protection rather than partial protection for a longer period.

Most laboratory tests used the yellow fever mosquito, *Aedes aegypti* (L.) or the stable fly, *Stomoxys calcitrans* (L.), reared under standard conditions and uniform in age and nutritional state. The repellents were applied at standardized dosages at prescribed intervals until bites were received. The CPT was the time between treatment and the first confirmed bite.

In field tests against mosquitoes and other biting flies, the test surfaces were based on the attack behaviour of the insects concerned. The purpose of some tests of repellent-treated jackets was to determine how well they prevented biting on the exposed *untreated* parts of the body, such as the face and hands, but other tests recorded landing rates on the treated garments themselves.

6.5.1.2 Fleas

The efficacy data found for repellents against fleas were all obtained in laboratory tests.

6.5.1.3 Ticks

Efficacy of repellents against ticks has usually been measured in ways that do not allow the ticks to actually bite humans. In laboratory tests, ticks were considered repelled if they failed to cross repellent-impregnated socks and attach to untreated legs above, or if they stopped, turned back or dropped off when they encountered a band of repellent-treated skin. Most field tests have involved people wearing garments impregnated or sprayed with the repellent and walking, standing, sitting or lying in tick-infested habitats for a set

period. The efficacy of the repellent has usually been estimated by comparing the numbers of ticks on the clothing and skin of subjects wearing treated garments with those wearing untreated garments.

6.5.1.4 Chiggers

Laboratory tests of repellents against chigger mites (Trombiculidae) were reviewed but no reports on field trials were found.

6.5.2 Criteria for inclusion of data

The aim was to include only data from trials on human subjects, with the dosages and test arthropods specified, and counts on untreated subjects to confirm biting pressure. Field trials were to be restricted to those in Canada or similar areas (e.g., northern U.S. and Russia), involving species known to occur in Canada, but some exceptions were made. Laboratory data for *Ae. aegypti* were included because it is the only mosquito against which almost all repellents have been tested, even though it does not occur in Canada. Since few reports of trials against biting midges and deer flies were found, only one of them conducted in Canada, the rules were relaxed to include trials in the southern U.S., trials with species not known to occur in Canada (e.g., *Chrysops atlanticus*), and trials with unidentified species. No reports of trials against chigger mites on humans were found, so the results of some in vitro tests have been included instead.

6.5.3 Dosages of active ingredients

The dosage of repellent at treatment depends on the volume of formulation applied, the area of skin treated and the concentration (weight per weight or weight per volume [w/v]) of active ingredient in the formulation. Dosages in milligrams active ingredient per square centimetre of skin (mg/cm^2) were required to group the results of similar trials. They were provided in many of the reports and were assumed to be correct. Where they were not provided, estimates had to be made, sometimes based on incomplete information.

For this re-evaluation, the main way of expressing dosages has been by the percentage of active ingredients, assuming that solutions are w/v and that 1.0 mL of product is applied and that the forearm area is 600 cm^2. To compare dosages of formulation in millilitres per arm with those of actives in mg/cm^2, the following formula was used:

Dosage in mg/cm^2 = (% active × 1000 mg) / (600 cm^2 × 100 mL) = (% active) / 60

A few laboratory tests used dosages as high as 5.0 mg/cm^2, but no other data were found where the dosage of active ingredient was higher than 1.67 mg/cm^2, the dosage obtained by applying 1 mL of an undiluted liquid repellent of specific gravity 1.00 to a forearm of 600 cm^2, although this upper limit is arbitrary and could easily be exceeded by putting on more repellent. Since the specific gravity of technical DEET is 1.00, the dosage obtained

by applying 1 mL of undiluted DEET will be exactly twice the dosage attained by applying 1 mL of a 50% w/v solution of DEET.

6.5.4 Processing of data

Efficacy was assessed by fitting generalized linear models to the CPT data (using the program GLIM 4.0, Numerical Algorithms Group Ltd., Oxford, U.K.). Each point reflected a mean CPT value for a treatment (dose) in a trial. The first step for each analysis was to fit each explanatory variable (DEET concentration, delivery mechanism and test location) to the CPT data, thereby yielding an estimate for that variable of influence on variance. Variables were then fitted in a stepwise fashion from the factor accounting for the most variance through to the factor explaining the least variance. The influences of two-way interactions were similarly assessed. The final model reflected that which was minimally adequate to describe the data. Specific forms of model fitted to CPT values were the general linear and quadratic ($y = a + mx + bx^2$), logarithmic ($y = a + b \ln(x)$) and inverse polynomial ($y = x / (a + bx)$).

6.5.5 Results

The results of 272 trials were included in the re-evaluation. The term “trial” is used here to mean a test or series of tests using the same repellent, formulation and dosage against the same pest colony or field population in the same place over the same period. Many of the reports reviewed include the results of several trials. The trials involved arthropods of at least 53 species (some reports did not include species identifications). Within each group of pests, there were not enough data to demonstrate consistent differences among individual species in their responses to any repellents, so data for several species were usually pooled (see notes on each group of pests, below).

Preliminary inspection of the data revealed great variations in the CPT values between subjects and trials at each concentration, but there were no consistent differences among the results for solutions, pressurized sprays, emulsions and towelette (wipe-on) formulations, so the results for these formulations were pooled for further analyses. The towelettes were treated as lotions with the same guaranteed percentages of active ingredient, even though the tissue paper is counted as an ingredient of the formulation. Pressurized spray (PP) formulations contain propellants that vapourize at the nozzle, so that the spray droplets that land on the user’s skin and clothing contain a higher concentration of active ingredients than the guarantee indicates. A survey of registered pressurized sprays in February 1998 showed that excluding the propellants from the formulations would be equivalent to raising the guarantees from 23.4 to 26.3% for 23 products containing DEET alone, from 10.0 to 11.1% for 3 products containing DEET + MGK 264 and from 30.1 to 38.6% for 9 products containing DEET + MGK 326 + MGK 264. Although pressurized sprays get more concentrated when sprayed, they had to be put in the pooled results according to concentrations of active ingredients before spraying, because most of the reports on trials of pressurized sprays did not state the percentages of propellants in the formulations.

6.5.5.1 Solutions, emulsions and pressurized sprays containing DEET only

6.5.5.1.1 Mosquitoes (Culicidae)

Most of the laboratory data (57 of 63 trials) were for *Ae. aegypti.* Although there were some data for *Anopheles quadrimaculatus* and *Culex quinquefasciatus*, there were not enough to demonstrate consistent differences among genera in their responses to any of the repellents tested.

Results of 55 field trials (received up to 1995) against mosquitoes in Canada (Manitoba, Ontario, Quebec), the U.S. and Russia were reviewed. Mosquitoes of at least 24 species in the genera *Aedes*, *Anopheles*, *Culex*, *Culiseta*, *Mansonia* and *Psorophora* were involved. *Aedes* mosquitoes (including those in the former subgenus *Ochlerotatus*, now elevated to the rank of genus) predominated in 89 of the studies; the most common species were *Ae. communis*, *Ae. canadensis*, *Ae. cinereus*, *Ae. excrucians*, *Ae. fitchii*, *Ae. sticticus* and *Ae. vexans*, all notorious pests in Canada. Most of the trials available for the re-evaluation involved several species of *Aedes*, and there were no clear differences between the responses of different species. Results for all *Aedes*, but not for mosquitoes of other genera, were included in the GLIM analysis. Most trials have been conducted by day, when it is easier to detect biting. This explains the scarcity of trials involving *Anopheles* and *Culex* mosquitoes, which bite mainly at night. It also means that the complete protection times are based on results for day-biting mosquitoes only, and personal repellents are also recommended for protection against night-biting mosquitoes, such as the *Culex* vectors of West Nile Virus.

DEET was the only repellent supported by several studies at each concentration over a wide range of concentrations against *Aedes* mosquitoes, and the results showed great individual variation. For example, the 15% formulations gave trial mean CPT values of 252–434 min and *individual* values of 206–528 min in field tests. Variation in the field data due to differences in species composition and weather could be expected, but the results of laboratory tests using *Ae. aegypti* under controlled conditions showed even more variation, with trial mean CPT values of 132–308 min, and *individual* values of 60–360 min.

For this re-evaluation, the results of laboratory tests (on *Ae. aegypti*) and field trials (on *Aedes* spp.) have been combined because the analysis revealed no significant differences between field and laboratory data. The relationship between CPT and DEET concentration was best described by a logarithmic function ($F_{1,100} = 146.1$, $P < 0.001$, $r^2 = 0.59$, Table 2). Hence, the CPT-dosage payoff declined with DEET concentration (see Table 3 and Fig. 1); quadratic and inverse polynomial models showed similar relationships. For example, the CPT predicted by the regression equation increased 3.5 times from 5 to 30% DEET, but only 1.5 times from 30 to 100% DEET. Thus, even though mean CPT at 100% DEET was substantially longer than at 25 or 50% DEET (677 ± 82 min, 344 ± 21 min and 427 ± 25 min, respectively; $P < 0.05$), the per unit DEET payoff expressed as CPT was substantially less: 6.7 min per % DEET for the 100% formulations, compared

with 8.5 min per % DEET for the 50% formulations and 13.8 min per % DEET for the 25% formulations (values predicted by the regression equation were much the same at 5.6, 9.1 and 14.1 min per % DEET, respectively). In other words, applying 25% DEET twice would provide longer protection than applying 100% DEET once (688 vs. 677 min), and with only half as much of the active compound. Indeed, applying 10% DEET three times would provide a substantial enhancement of protection time (735 min) with less than one third of the dosage of active ingredient.

The payoff may be even more pronounced in the typical summer field setting for Canada, where day length can be 15–16 h, with mosquitoes often biting in the hours surrounding dawn and dusk. A single application of 100% DEET would not provide sufficient coverage in this scenario (i.e., only 10–11 h), and reapplication would be required through the day. Hence, given that two applications of 10 or 25% DEET might convey adequate protection in these circumstances, total DEET usage could be as much as 10× higher with the 100% formulation (2× 100% applications vs. 2× 10% applications). There are no data to show that concentrated DEET products are essential for protection against mosquitoes.

Table 2. Relationships between the CPT and DEET concentration for human subjects exposed to biting flies. Linear and quadratic (CPT = $a + mx + bx^2$), logarithmic (CPT = $a + b \ln(x)$) and inverse polynomial (CPT = $x / (a + bx)$) models are shown. x, DEET concentration; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; % values > 50, proportion of records that were obtained at DEET concentrations exceeding 50%.

Insect	Model		R^2	% values > 50
***Aedes* mosquitoes** (57 lab and 55 field trials)	Quadratic	$131 + 8.5x - 0.034x^2$***	0.56	7.8
	Logarithmic	$-133.6 + 151 \ln(x)$***	0.59	
	Inverse polynomial	$x / (0.03556 + 0.0014x)$***	0.58	
Stable flies (22 lab trials)	Linear	$116.8 + 4.7x$***	0.5	4.5
	Logarithmic	$-183.1 + 141.7 \ln(x)$***	0.58	
	Inverse polynomial	$x / (0.06477 + 0.0012x)$***	0.58	
Black flies (25 field trials)	Linear	$213.8 + 3.2x$***	0.34	12.0
	Logarithmic	$-22.4 + 106.5 \ln(x)$**	0.26	
	Inverse polynomial	$x / (0.01764 + 0.00237x)$	0.1	
Biting midges (14 field trials)	Linear	$92.7 + 4.6x$***	0.93	21.0
	Logarithmic	$-227.4 + 158.3 \ln(x)$***	0.84	
	Inverse polynomial	$x / (0.05626 + 0.0015x)$***	0.92	
Deer flies (11 field trials)	Linear	$18.1 + 1.8x$**	0.56	27.0
	Logarithmic	$-180.6 + 80.0 \ln(x)$*	0.5	
	Inverse polynomial	$x / (0.2901 + 0.0024x)$***	0.64	

Fig. 1. Plot of the logarithmic function $y = a + b \ln(x)$ of CPT of DEET against *Aedes* mosquitoes, where y is the CPT in minutes and $\ln(x)$ is the natural logarithm of the % concentration of technical DEET. Circles, trial means; solid line, values predicted by regression equation. The function was not affected by experimental location (field vs. laboratory; $F_{1,99} = 0.4$, $P > 0.05$) or application methodology (liquid suspensions or solutions vs. pressurized sprays; $F_{1,97} = 0.3$, $P > 0.05$).

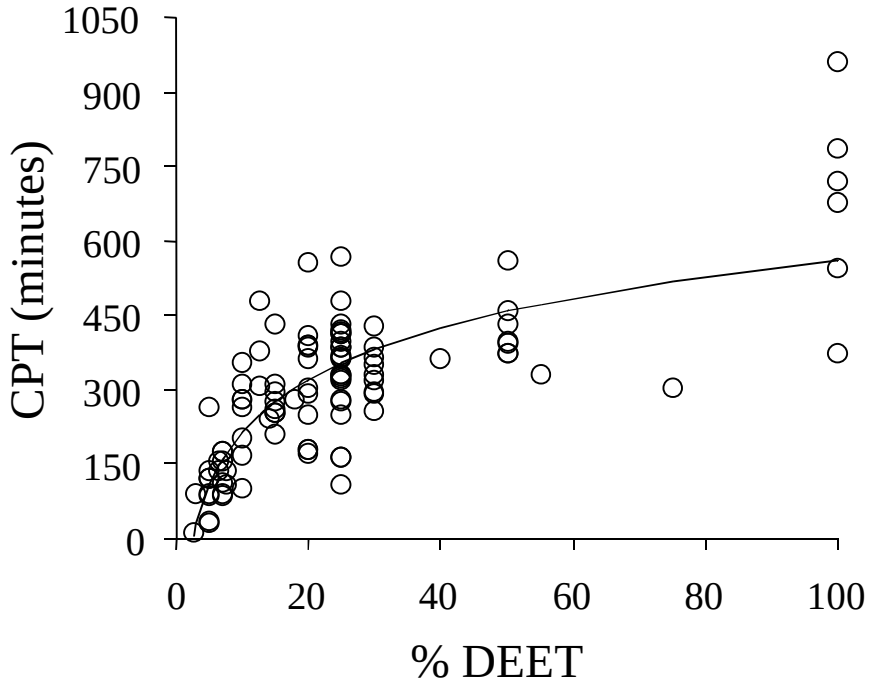


Table 3. Calculated CPT values for 5–100% DEET against *Aedes* mosquitoes, from the logarithmic function $y = a + b \ln(x)$, where y is the CPT in minutes and hours and $\ln(x)$ is the natural logarithm of the % concentration of technical DEET.

% DEET	Complete protection time					
	Mean		Lower residual		Upper residual	
	Minutes	Hours*	Minutes	Hours*	Minutes	Hours*
5	110	2	76	1.5	144	2.5
10	214	3.5	158	2.5	270	4.5
15	276	5	208	3.5	344	5.5
20	319	5.5	243	4	395	6.5
25	352	6	269	4.5	469	8
30	380	6.5	281	5	469	8

% DEET	Complete protection time					
	Mean		Lower residual		Upper residual	
	Minutes	Hours*	Minutes	Hours*	Minutes	Hours*
40	424	7	326	5.5	522	8.5
50	458	7.5	354	6	562	9.5
75	519	9	402	6.5	636	10.5
100	562	9.5	437	7.5	687	11.5

*Rounded off to the nearest half hour

Precise protection time claims, ranging from 1 to 8 h, are on the labels of a few of the DEET EPs. The labels of others have vaguer claims (e.g., “lasts for hours,” “super long-lasting protection”). Very few products have original data to support such claims, and none of the products that claim repellency against several groups of pests give any indication of possible differences in protection times between the different groups of pests.

There are two advantages to having expected protection times against mosquitoes required on labels. First, they give users an indication of what they may expect from a product, and it allows for comparison among products. Second, they will also allow comparisons between repellents containing DEET and repellents containing other active ingredients.

There are also two disadvantages of expected CPT values on labels. First, there is too much variation among people to make the values reliable. Second, it might encourage unnecessary use if people automatically reapplied DEET at the end of the expected CPT, regardless of whether the previous application was still effective, or the mosquitoes were still active. This problem will be addressed by including the statement: “Reapply after *x* hours if necessary,” where *x* is the expected CPT.

Conclusion

Although there are great variations in CPT values for DEET on different individuals against mosquitoes, we have enough field data relevant to Canada to allow expected CPT values for solutions, emulsions and pressurized sprays with more than 5% DEET (Table 2, Fig. 1), without reviewing any more product-specific data, provided that the formulations proposed for registration are equivalent to those of the products already registered. Expected CPT values may be read from the regression line or calculated from the equation. Any applicant applying to register a repellent with a standard formulation and wishing to claim a longer CPT will have to supply product-specific efficacy data. Products with more than 30% DEET are not essential for protection against mosquitoes.

6.5.5.1.2 Stable flies (Muscidae)

The results of 26 laboratory trials against stable flies (*Stomoxys calcitrans*) were reviewed. Almost all the tests were conducted at the laboratories of one registrant, according to a standard protocol. Only one field trial, in Florida, was found.

The response of stable flies to DEET was similar to that shown by mosquitoes, with both the logarithmic and inverse polynomial functions providing the best fit to the data ($F_{1,20} = 28$, $P < 0.001$, $r^2 = 0.58$; see Table 2). Apart from the elevated CPT value at 100% DEET, efficacy appeared to reach a maximum between 20 and 30% DEET. Because values are absent between 50 and 100% DEET, more detailed assessments were impossible.

6.5.5.1.3 Black flies (Simuliidae)

Results of 22 field trials against black flies in Canada (Labrador, Ontario, Quebec), the U.S. (Maine, Massachusetts, New York) and Russia (Karelia, Krasnoyarsk Krai) were reviewed. Black flies of six species were identified; the most frequently mentioned were *Simulium venustum* (actually a complex of species, within which the major pests are *S. venustum* s.s. and *S. truncatum*) and *Prosimulium mixtum*. The test methods were generally the same as for mosquitoes.

The CPT against black flies was best described by the linear function CPT = 213.8 + 3.2 DEET concentration ($F_{1,24} = 12.7$, $P < 0.05$, $r^2 = 0.34$; see Table 2 and Fig. 2). As with mosquitoes, the CPT-dosage payoff declined with DEET concentration. For instance, the predicted CPT at 25% DEET was 294 min, or 55% of the CPT at 100% DEET. Therefore, as with mosquitoes, two applications of the 25% formulation would provide longer protection than a single application of the 100% formulation, and with only half as much of the active compound.

Because only three estimates of CPT were available for concentrations greater than 40% DEET (all for 100% DEET), analyses were redone without these values. When this was done, there was no relationship between DEET concentration and CPT ($F_{1,21} = 0.1$, $P > 0.05$). In other words, the CPT against black flies for 7% DEET was statistically indistinguishable from the CPT against black flies for 100% DEET (CPT = 253 min), therefore suggesting that very low concentrations of DEET would provide adequate protection from black flies.

6.5.5.1.4 Biting midges (Ceratopogonidae)

The least ambiguous common names for bloodsucking adult Ceratopogonidae are ‘biting midges’ in English and ‘brûlots’ in French, and it would be best if only these names were used on product labels for Ceratopogonids, though ‘no-see-ums’ in the English would be an acceptable synonym. Unfortunately, the labels of 41 products use the names ‘sand flies’ or ‘midges’ where Ceratopogonids were probably intended. Biting female Ceratopogonids

are called just ‘midges’ in Britain. ‘Sand flies’ is widely used in English-speaking countries for Phlebotomines (Psychodidae), which are vectors of leishmaniasis and other diseases, but rarely found in Canada and not known to be vectors or pests here, so this name should not be used on Canadian product labels. ‘Phlebotomes’ was used in the French label text of three products (in 1995) where the English text had ‘sand flies.’ ‘Midges’ (‘Moucherons’ in French) is also the common name for adult Chironomidae, which can be a nuisance when abundant (e.g., around lights at night), but they do not suck blood and there is no evidence that personal repellents would be effective against them.

Results of 14 field trials against biting midges in the U.S. (Florida, Georgia, South Carolina) and Russia (Karelia) were reviewed. No studies in Canada were found, and all the studies in the U.S. were in southern states. Of the eight species of biting midges identified in the trials, only three (*Culicoides canithorax, C. hollensis* and *C. melleus*) have been recorded in Canada. The test methods used were the same as those for mosquitoes.

The CPT against biting midges appeared to increase with DEET concentration (Table 2, Fig. 2), but there were too few trials (14) for detailed analyses.

6.5.5.1.5 Deer flies and horse flies (Tabanidae)

Results of 12 field trials against deer flies (*Chrysops* spp.) and horse flies (*Tabanus* spp.) in Canada (Quebec), the U.S. (Georgia, New Jersey, Oregon) and Russia were reviewed. Three of the four species identified (*C. discalis, Tabanus lineola* and *T. nigrovittatus*) are known to occur in Canada, but *C. atlanticus*, the only species involved in most of the trials, is not. The test methods used were the same as those for mosquitoes. DEET was tested over a range of concentrations against deer flies, with generally poor results.

The CPT against deer flies appeared to increase as a linear or polynomial function of DEET concentration (Table 2) but, as with the data for biting midges, the small number of trials (11) precludes detailed analyses.

Conclusions

The data available for stable flies, black flies, biting midges and deer flies suggest that the protection time increases with DEET concentration, but are not sufficient to determine expected CPT values for each pest group and DEET concentration. More efficacy data applicable to Canada would be required.

6.5.5.1.6 Fleas (Siphonaptera)

Only three reports on laboratory tests of DEET against fleas were found, and only one of them included tests where the DEET was applied directly to the skin.The arms of five of six subjects were bitten immediately after treatment; the sixth subject was bitten 1 h after treatment.

Conclusion

The claim to repel fleas, which is now on the labels of 67 DEET products, can no longer be accepted until better data to support it are provided and reviewed.

6.5.5.1.7 Ticks (Acari: Ixodidae)

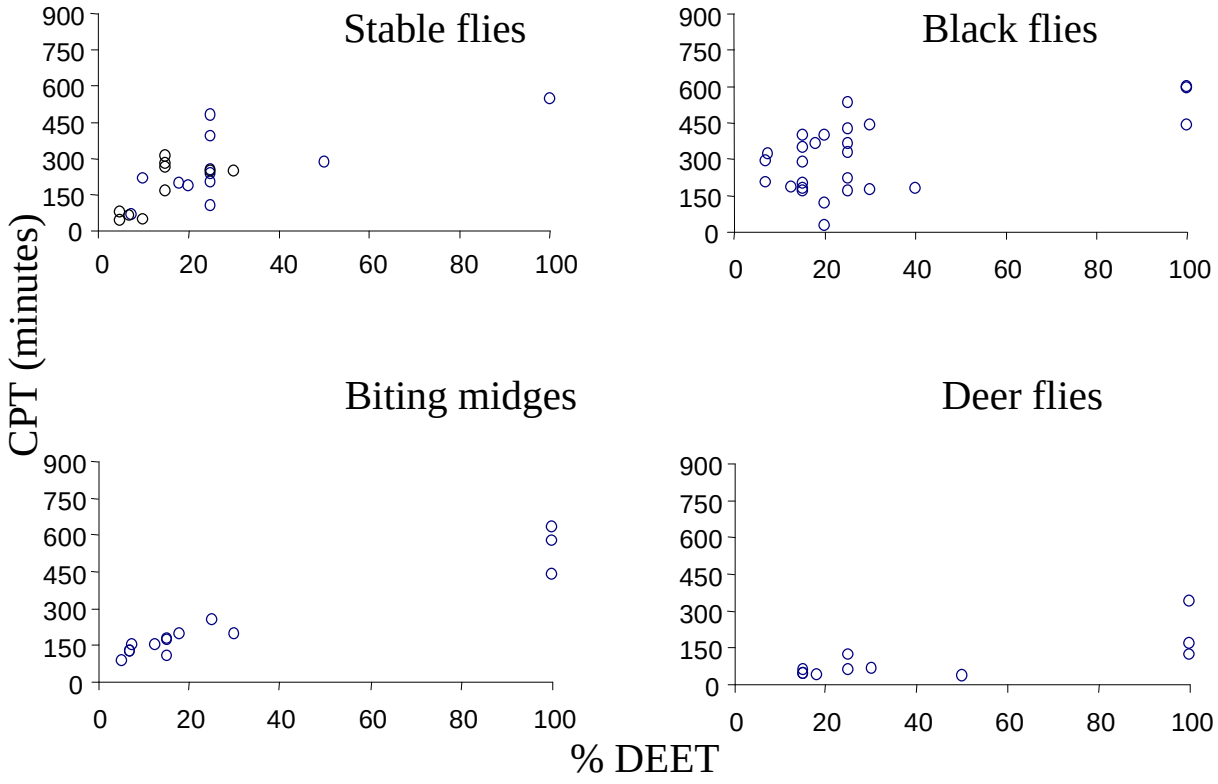
Data from 17 laboratory trials and 12 field trials of repellents against nymphal and adult ticks were found, all of them in the U.S. (Maryland, Massachusetts, New Jersey, Oklahoma). Results were usually expressed as percent repellency at various times after treatment, and are difficult to compare because of differences in the method of treatment (directly on skin, sprayed clothing, impregnated clothing), efficacy criteria, and the species and stage of the ticks (adults, nymphs, larvae).

Most of the field data were for the lone star tick (*Amblyomma americanum*), which is rarely found in Canada. The American dog tick (*Dermacentor variabilis*), the brown dog tick (*Rhipicephalus sanguineus*) and the blacklegged tick (*Ixodes scapularis*, also known as the deer tick, *I. dammini*) are more common in Canada, but there are fewer field data for them. Some registrants have wanted to include specific claims on labels that their products repel the blacklegged tick, because it is a vector of Lyme disease. There are laboratory data showing that DEET on the skin is about equally effective against lone star, American dog, brown dog and blacklegged ticks, and field data showing its effectiveness against lone star ticks, from which we may suppose that it would be equally effective against the other ticks, but Canadian field data to confirm this would be needed. There are more field data on the efficacy of DEET-treated garments.
Laboratory tests against *I. scapularis* gave CPT values of 250 min for 35% DEET and 375 min for 70% DEET. Data from laboratory tests with 15% and 40% DEET against *A. americanum*, *I. scapularis* and *R. sanguineus* indicate 90–100% repellency at 4 h after application. Conversely, 40% DEET pressurized spray was only partially effective against *D. variabilis, I. pacificus* and *R. sanguineus* adults at 3 h after application, less than would have been expected. The inconsistent results in this study may have been due to using numbers of ‘touches’ (presumptive bites) as the index of repellency.

In a field trial in Oklahoma, the percent repellency of 12.5, 15, 25, 30, 40, 50 and 100% DEET solutions was measured against lone star ticks (*Amblyomma americanum*) at 4, 6, 10 and 12 h after application. At 10 h after application, 30, 40, 50 and 100% DEET were still giving 92–100% protection. The lower concentrations of DEET were not as effective, but 12.5% gave 93% protection at 1 h, 15% gave 100% protection at 4 h and 25% gave 92% protection at 6 h. In another field study against *A. americanum* in the U.S. (New Jersey) using 25% DEET, the percent protection was only 90% at 0–30 min and 87% at 240–270 min after application. In both studies, DEET solutions of 25% and up continued to give high levels of partial protection (greater than 70%) long after they had ceased to give complete protection.

Conclusions

Fig. 2. CPT values against DEET concentration for stable flies (laboratory tests), black flies (field trials), biting midges (field trials) and deer flies (field tests).



There are sufficient laboratory data to show that DEET repels *D. variabilis, I. scapularis* and *R. sanguineus*, all of them important ticks in Canada, but insufficient CPT data for DEET against any ticks to perform a regression analysis, and no field data for Canada. The claim that DEET products repel ticks (in general) should continue to be allowed, but expected CPT values cannot be provided until more field data applicable to Canada are available.

6.5.5.1.8 Chigger mites (Acari: Trombiculidae)

The accepted common names for the bloodsucking larva of a Trombiculid mite are ‘chigger’ in English and ‘aoûtat’ or ‘rouget’ in French. The bilingual labels of some products have ‘chiggers’ in the English text and ‘chiques’ in the French. ‘Chique’ is the French common name for the tropical flea *Tunga penetrans*, also called ‘chigger’ or ‘jigger’ in English. *Tunga penetrans* does not occur in Canada, and we have no evidence that personal repellents would protect people against it, so the use of ‘chiques’ on French labels should be discontinued.

The efficacy of repellents against chiggers has generally been assessed by knockdown and kill of larvae on treated fabrics rather than by prevention of bites on treated skin. Laboratory tests of DEET on fabric against chiggers of two species, *Eutrombicula alfreddugesi* and *E. splendens*, both of them known to occur in Canada, were reviewed. *Eutrombicula splendens* larvae placed on skin that had been treated with 5% DEET solution 4 h earlier all became moribund within 5 min. Glass or fabric treated with 15% DEET repelled larvae of *E. alfreddugesi* or knocked them down rapidly, and 46-d-old deposits of 100% DEET on cotton fabric knocked down *E. splendens* larvae after less than 15 min exposure. We have no data on efficacy under Canadian field conditions.

Conclusions

Claims to repel chiggers are on the labels of 38 DEET products (Table 1), even though they are not common pests in Canada. It would be useful to have data demonstrating the efficacy of DEET against chiggers in the field, but the small size of these mites makes field testing impractical. The laboratory data showing that exposure to DEET immobilizes chiggers are an acceptable substitute. This use may therefore be retained.

6.5.5.2 Extended duration formulations

DEET has been incorporated into microencapsulated, microparticulate and polymer formulations to increase the protection time by reducing loss from the skin surface due to absorption, evaporation and abrasion. In laboratory tests, an extended duration (ED) formulation containing 33.75% DEET had a CPT of greater than 600 min against *Ae. aegypti*. A DEET solution of the same concentration in alcohol would have an expected CPT of 398 min, using the logarithmic equation for mosquitoes (Table 2). An ED formulation containing 33% DEET has been registered in Canada and has been field tested against mosquitoes and black flies. The mean CPT against mosquitoes was 496 min, 102 min longer than the expected CPT for a 33% DEET solution (394 min), and the mean CPT against black flies was 462 min.

Conclusions

The efficacy data available would allow an expected CPT value of 8.5 h against mosquitoes for the currently registered ED products.

6.5.5.3 DEET-treated garments[3]

A hooded jacket to be impregnated with DEET was registered in Canada until 2000. It was made of an absorbent netting material, designed to be worn over other clothing, and was supplied with a bottle of undiluted technical DEET for impregnation and re-impregnation of the jacket by the user. An efficacy claim was implied on the product label

[3] No DEET-treated garments are currently registered. However, since such products had been registered until recently, an efficacy assessment is presented for completness.

("Re-charge after 32 h of use, or if effectiveness wears off"), but the registrant sent no efficacy data.

In laboratory tests, samples of army uniform or cotton stocking material were impregnated with DEET and tested at intervals after impregnation by using them to cover the arms or legs of human subjects who were exposed to biting arthropods. In such tests, DEET remained repellent to *Ae. aegypti* females for 39 days after impregnation at 2.2 mg/cm^2 and for 46 days after impregnation at 3.5 mg/cm^2. These results are impressive, but not necessarily good indicators of how long DEET-impregnated garments would repel mosquitoes in the field.

Only a few field trials against mosquitoes and black flies in Canada were found, most of them conducted by the Department of National Defence to test repellent jackets for use by armed forces personnel. The results showed that mesh jackets freshly impregnated with 0.25 g of DEET per gram of fabric repelled more than 90% of mosquitoes and black flies from landing on the jackets themselves, and one study reported a 92% reduction in the numbers biting the exposed faces of the wearers. In the only two studies that continued beyond the first day of use, the one in Alaska found greater than 95% repellency against mosquitoes at 7 days after impregnation, and the one at Fort Drum, N.Y., found a mean of 98% repellency against black flies over 5 successive days of jacket use. There are other reports of long-lasting repellency of treated garments, such as the 92% repellency of a DEET-treated suit to black flies in Russia, 19 days after treatment.

Conclusions

Enough data are available to support the claim that DEET-impregnated jackets repel mosquitoes and black flies, but not enough data to justify claims of any specific period of complete protection. The jackets were impregnated with undiluted technical DEET. Since products containing more than 30% DEET will no longer be allowed (Section 5.3), data showing efficacy of the jackets after impregnation with 30% DEET or less would be required should anyone wish to register such a product. Reimpregnation intervals, based on the submitted data, would have to be added to the labels. It would also be useful to have data to show if the jackets prevent biting on the uncovered faces and hands of wearers.

6.5.5.4 DEET+sunscreen products

In laboratory trials against *Ae. aegypti*, an application of DEET at 15, 45, 75 or 105 min after the application of a sunscreen (sun protection factor [SPF] 15) to human skin reduced the efficacy of the sunscreen by 33.5% on average (Montemarano, A.D., et al. 1997. Insect repellents and the efficacy of sunscreens. *The Lancet*, **349**: 1670–1671), but application of a sunscreen before, at the same time as, or after DEET did not reduce the efficacy of the DEET (Murphy, M.E. et al. 2000. The effect of sunscreen on the efficacy of insect repellent: A clinical trial. *Journal of the American Academy of Dermatology*, **43**: 219–222). The results of the latter study conflict with those in an unpublished report

submitted by a registrant of DEET products, which found that simultaneous application of a sunscreen (SPF 15) with a 15% DEET lotion to human arms did reduce the mean CPT against *Ae. aegypti* from 130 to 5 min when compared with the 15% DEET lotion alone.

In 1998, members of the DEET Joint Venture submitted 10 reports on the efficacy of DEET+sunscreen products, 5 of them on laboratory tests against mosquitoes, 2 on laboratory tests against ticks and 1 report each on field tests against mosquitoes, black flies and biting midges. In four of the five lab trials against mosquitoes (*Ae. aegypti*) and both trials against blacklegged ticks (*Ixodes scapularis*) in the lab, the CPT for formulations with DEET and sunscreen was longer than the CPT for formulations with DEET only. In field trials with a 7.5% DEET+sunscreen product, the CPT against mosquitoes was shorter than the expected CPT for 7.5% DEET alone, but the CPTs for black flies and biting midges were longer than expected values for DEET alone. While the results of these trials indicate that, in most cases, the DEET+sunscreen product was more effective than DEET alone, there are not enough data to be certain that the addition of a sunscreen (several different compounds are used) could never reduce the efficacy of DEET.

Conclusion

DEET+sunscreen combination products can no longer be allowed because of conflicting use instructions for the repellent and the sunscreen (see Section 5.3). If the safety of such products could be demonstrated, it would also be prudent to require product-specific efficacy data until more is known about the effects of the various sunscreens on repellent performance.

6.5.5.5 Other pest names on labels

The following insect names are still found on the labels of one or more registered DEET EPs, but no data or other justifications have been found to support their use.

Gnats: ‘Gnat’ is an archaic English synonym for mosquito or black fly (as in ‘buffalo gnat’), but its use on labels is confusing, and also redundant when the products also claim to repel mosquitoes and black flies, as many of them do.

Sand flies and Midges: See discussion on biting midges under Section 6.5.5.1.4.

Biting flies, Flies, and Biting insects: These terms are broader than the available efficacy data could support for any product, and should no longer be allowed on labels, even though some users may neither know nor care just what sort of insect they are confronted with. (The use of “insect repellent” in the product name already allows some user discretion in practice.)

Chiques: See discussion on chigger mites under Section 6.5.5.1.8.

Moucherons: See discussion on biting midges under Section 6.5.5.1.4.

Cousins: Bélisle (1979. *Dictionnaire Nord-Américain de la langue française*) defines 'Cousin' as "Maringouin: Moucheron dont la piqure est fort incommode." 'Cousin' might be an acceptable alternative to 'moustique' or 'maringouin' as the French translation of 'mosquito,' but only one of these should be the primary name on any French label (with synonyms in parentheses, if needed).

Conclusion

All the names listed above in this section should be deleted from labels of DEET products.

6.6 Current pest management strategies

Products registered under the PCPA for personal protection against mosquitoes and other biting flies include personal repellents, space sprays and mosquito coils for use indoors, and yard foggers. A number of products are registered for premise treatment against flea larvae and ticks. Nonchemical protection methods include clothing (e.g., head nets), screens and timing one's activities to avoid exposure to bloodsucking arthropods.

Registered products for community protection against biting flies include larvicides (e.g., organophosphates, insect growth regulators and *Bacillus thuringiensis*) for use against mosquito and black fly larvae, space sprays, fogs and residual premise sprays (e.g., pyrethrum and synthetic pyrethroids) for use primarily against adult mosquitoes. Nonchemical methods for community protection include habitat modification to control mosquito and black fly larvae, and manure management to control stable fly larvae.

6.7 Potential alternative pest management strategies

As of August 1, 2001, there are 16 registered personal repellent products that do not contain DEET. Twelve of them contain one or more essential oils as active ingredients (3 products with oil of citronella, 1 with citronellal, 1 with oil of lavender and 5 with blends of natural or artificial essential oils). These active ingredients are also under re-evaluation. Four personal repellents containing soybean oil as the active ingredient were granted registration in Canada in 2000, but are not currently marketed.

Products containing *p*-menthane-3,8-diol (extract of lemon eucalyptus leaves) or piperidine compounds as active ingredients show promise as dermally applied mosquito or black fly repellents and are available commercially in other countries, but not registered in Canada.

7.0 Regulatory conclusions

7.1 DEET

7.1.1 Safety

7.1.1.1 Adults and individuals older than 12 years of age

Products containing DEET at concentrations above 30% will no longer be acceptable for registration, based on a human health risk assessment that considered daily application of DEET over a prolonged period of time. There are also no data that show that more concentrated DEET products are essential for protection against any blood sucking arthropods. Studies show that products with lower concentrations of DEET are as effective as the high concentration products, but they remain so for shorter periods of time. Products containing no more than a 30% concentration of DEET will provide adults with sufficient protection.

7.1.1.2 Children

- Children under 6 months of age
    - DO NOT use personal insect repellents containing DEET on infants.
- Children aged 6 months to 2 years
    - In situations where a high risk of complications from insect bites exist, the use of one application per day of DEET may be considered for this age group.
    - The least concentrated product (10% DEET or less) should be used.
    - The product should be applied sparingly and not be applied to the face and hands.
    - Prolonged use should be avoided.
- Children between 2-12 years of age
    - The least concentrated product (10% DEET or less) should be used.
    - Do not apply more than three times per day. Do not apply to the face and hands.
    - Prolonged use should be avoided.

7.1.2 Efficacy

- Enough data for mosquitoes are available to support reapplication intervals and expected CPT values on the labels of solutions, emulsions and pressurized sprays containing 5–30% DEET (Table 2, Fig. 1), provided the formulations are

equivalent to those of the products already registered. Expected CPT values may be read from the regression line or calculated from the equation. Any registrant wishing to claim a longer CPT will have to provide product-specific efficacy data.

- There are enough data to confirm that DEET repels black flies, biting midges, deer flies, stable flies and ticks, but not enough to predict the CPT for DEET against them. Laboratory data showing efficacy of DEET against chigger mites are acceptable.

- There are no data to show that products with more than 30% DEET are essential for protection against any bloodsucking arthropods.

- There are not enough data to confirm that DEET is a useful repellent against fleas.

- Some of the pest names on the labels of DEET products are vague, ambiguous or incorrect.

7.2 DEET+sunscreen products

It is generally recommended that DEET products be applied sparingly while sunscreens should be applied liberally and frequently to ensure adequate protection from the sun. For combination products that contain both DEET and sunscreens, a risk assessment based on liberal application provided an inadequate MOE for DEET exposure. The use of these products sparingly, however, does not provide adequate protection against the sun and is not in compliance with Health Canada's Category IV Monograph for Sunburn Protectants (www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/cat4/sunbupro_e.html). Therefore, based on these incompatible methods of application the use of these DEET+sunscreen combination products will no longer be acceptable for registration.

8.0 Label changes

8.1 Safety

Standard label statements reflecting the decisions are outlined in Appendix I. They include standardized precautionary and first aid statements as well as clearly defined directions regarding the application of the products.

8.2 Efficacy

- The reapplication interval, based on the regression equation for expected CPT against mosquitoes, to the nearest hour, **must** be on the labels of all products. The wording will be: "Reapply after *x* hours if necessary," where *x* is the expected CPT. Calculated CPT values for products containing 5 – 30% DEET are presented in Appendix I.

- A protection time claim, also based on the regression equation for expected CPT against mosquitoes, **may** also be on the labels of products (it is optional), if space permits. If a protection time claim is included, the wording will be: "Repels mosquitoes for *x* hours. Also repels black flies, biting midges, deer flies, stable flies, ticks, chiggers." (Any or all of these names are acceptable.) If no protection time is included, the wording will be: "Repels mosquitoes, black flies, biting midges, deer flies, stable flies, ticks, chiggers." (Any or all of these names are acceptable.) Expected CPTs longer than the regression equation values for mosquitoes, or expected CPTs for other pests, will have to be supported by product-specific efficacy data. The use of data already submitted for registered products to support CPTs longer than those predicted by the DEET concentration will be negotiated with individual registrants on a case-by-case basis.

- Claims to repel fleas must be deleted.

- The following vague, ambiguous or incorrect pest names must be removed from the labels unless registrants can provide acceptable arguments that inclusion of the names in question is needed for effective use of the products: 'biting flies,' biting insects,' 'flies,' 'gnats,' 'midges' and 'sand flies' from the English labels; 'chiques,' 'cousins,' 'frelons,' 'insects piquants,' 'mites,' 'moucherons,' 'mouches,' 'mouches piquants,' 'mouches des sables,' 'phlebotomes,' 'thrips' and 'tique brune du chien' from the French labels.

9.0 Data deficiencies

9.1 Chemistry data

9.1.1 TGAI

- CPSF in accordance with Table 1 in Section 2.12 of DIR98-04. The guarantee of the TGAI corresponds to the nominal purity provided.

- Validation data for the analytical method used to determine the active ingredient.

- Analytical data from five recent batches of the TGAI to 0.1% as per Section 2.13.3 of DIR98-04 to support the revised CPSF.

9.1.2 EPs

CPSFs for all registered EPs that will continue to be registered, in accordance with Table 1 in Section 3.3 of DIR98-03. The nominal value of the active ingredient in the revised CPSF must correspond to the label guarantee for the EP.

9.2 Efficacy and value data

No other efficacy data are required at this stage. A90-01 asked registrants to supply data to support all uses. Some uses (e.g., fleas) are not supported by data supplied by the registrants, nor by the literature survey, and the DITF was informed of the data gaps in 1998. Any uses still not supported will have to be deleted from the labels. Registrants will have to make submissions, with the required data, to reinstate these uses.

10.0 Implementation

The PMRA has notified registrants of end-use products of the regulatory conclusions and decisions outlined in this document. The decisions are to be implemented as follows:

10.1 Existing products containing >30% DEET

The distribution and sale of products which contain more than 30% DEET will be phased out through voluntary discontinuation of sales or suspension of registrations. Registrants have been given the option to voluntarily discontinue sale of these products in accordance with section 16 of the regulations under the *Pest Control Products Act.* The effect of the voluntary discontinuation would be that product could be sold by registrants until August 31, 2002. Sale after August 2002 by registrants would be prohibited. Retail sale of products containing more than 30% DEET could take place until December 31, 2004. To date, most registrants have informed the PMRA of their intention to discontinue sales of products containing greater than 30% DEET in accordance with the schedule. Where a registrant chooses not to submit notification of intent to discontinuation of sales, action will be taken under authority of section 20 of the regulations to suspend the affected registration. Such action will terminate the registrant's right to sell the product as of the date of the suspension.

10.2 Existing combination DEET + sunscreen products

The distribution and sale of combination DEET + sunscreen products will be phased out through voluntary discontinuation of sales or suspension of registrations. Registrants have been given the option to voluntarily discontinue sale of these products in accordance with section 16 of the regulations under the *Pest Control Products Act.* The effect of the voluntary discontinuation would be that product could be sold by registrants until August 31, 2002. Sale after August 2002 by registrants would be prohibited. Retail sale of combination DEET + sunscreen products could take place until December 31, 2003. To date, most registrants have informed the PMRA of their intention to discontinue sales of combination DEET + sunscreen products in accordance with this schedule. Where a registrant chooses not to submit notification of intent to discontinuation of sales, action will be taken under authority of section 20 of the regulations to suspend the affected registration. Such action will terminate the registrant's right to sell the product as of the date of the suspension.

10.3 Existing products containing 30% or less DEET

Registrants of personal insect repellents containing 30% DEET or less who wish to continue with registration are required to amend the registration in accordance with the new labelling requirements (Appendix I). Product manufactured for sale in 2003 and beyond must be labelled according to the new requirements. Retail sale of currently labelled product (i.e., product with existing label) could take place until December 31, 2004.

Registrants who do not wish to have a registration continued have been given the option to voluntarily discontinue sale of these products in accordance with section 16 of the regulations under the *Pest Control Products Act*. The effect of the voluntary discontinuation would be that currently labelled product could be sold by registrants until August 31, 2002. Sale after August 2002 of currently labelled product by registrants would be prohibited. Retail sale could take place until December 31, 2004.

To date, most registrants have either made application to amend the registration of their product containing 30% or less DEET, or have informed the PMRA of their intention to discontinue sales of their product.

Where registrants choose not to amend a registration or to give notice of discontinuation of sales as indicated above, action will be taken under section 20 of the regulations to suspend the affected registration. Such action will terminate the registrant's right to sell the product as of the date of the suspension.

10.4 New products containing 30% or less DEET

The PMRA is prepared to accept applications to register new products which contain DEET at a concentration of 30% or less provided that the products conform with the labelling statements indicated in Appendix I.

The decisions outlined in this Decision Document conclude the re-evaluation by PMRA of the use of DEET in personal insect repellent products.

List of abbreviations

a.i.	active ingredient
BPA	Bureau of Pharmaceutical Assessment
bw	body weight
CAS	Chemical Abstracts Service
C_{max}	peak plasma concentrations
CPSF	control product specification form
CPT	complete protection time
d	day(s)
DEET	*N*,*N*-diethyl-*m*-toluamide, diethyl toluamide or DTU
DITF	DEET Issues Task Force
ED	extended duration
EP	end-use product
EPA	Environmental Protection Agency
F_1	first generation offspring
F_2	second generation offspring
h	hour(s)
K_{ow}	*n*-octanol–water partition coefficient
min	minute(s)
MOE	margin of exposure
NOAEL	no observed adverse effect level
PCPA	*Pest Control Products Act*
SAP	Scientific Advisory Panel
SPF	sun protection factor
TGAI	technical grade active ingredient
U.S.	United States
w/v	weight per volume

Appendix I: Required Label Statements for End-Use Products

Label	All Products, All Concentrations	Products with 11 -- 30% DEET	Products with ≤10% DEET	Aerosol and Pump Products
Use Directions	• Apply sparingly not under clothing and only when necessary. • Reapply after X hours if necessary[4] • EITHER: Repels mosquitoes for X hours[1]. Also repels black flies, biting midges, deer flies, stable flies, ticks, chiggers [any or all of these names are acceptable] OR: Repels mosquitoes, black flies, biting midges, deer flies, stable flies, ticks, chiggers [any or all of these names are acceptable][5]			• TO APPLY TO FACE: Spray hands and apply avoiding eyes and mouth. • Do not spray in enclosed spaces.
Precautions	• Avoid contact with eyes and mouth (separate instructions under aerosol products)	• Do not use on children under 12 years of age.	• Supervise applications on children. • Do not use on infants under 6 months of age. • In 6 month to 2 year olds, do not apply more than once a day. Not for daily use. Avoid application to hands. • In 2-12 year olds, Do not apply more than 3 times per day.	

4 See table entitled “Calculated Complete Protection Time (CPT)” values for 5-30% DEET against mosquitoes.” Any reapplication intervals or protection times different from those indicated in Appendix I would have to be supported by data or scientific rationales in a submission to PMRA.

5 The use on labels of any pest names other than those in Appendix I would have to be supported by data or scientific rationales in a submission to PMRA.

Label	All Products, All Concentrations	Products with 11 -- 30% DEET	Products with ≤10% DEET	Aerosol and Pump Products
First Aid	• If in eyes: Remove contact lenses, and flush with water for 15 minutes. • If irritation or other adverse effects develop wash with soap and water immediately. Seek medical attention if symptoms persist. Always take container label with you when seeking medical attention.			If inhaled: Give artificial respiration if indicated. Seek medical attention.

Calculated Complete Protection Time (CPT) values for 5-30% DEET against mosquitoes

% DEET Technical	Calculated complete protection time (CPT) in hours
5-6 % DEET	2 hours
7-10% DEET	3 hours
11-14% DEET	4 hours
15-21% DEET	5 hours
22-30% DEET	6 hours