

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DEET IN THE UNITED STATES

Technical DEET is a nearly colorless liquid with a faint characteristic odor. It is mainly used as a commercial insect or acarid repellent. In 1990, approximately 4 million pounds of the active ingredient DEET was used in commercial products and the average annual domestic use of DEET has been estimated as ranging from 5 to 7 million pounds based on product sales. Aquatic systems appear to be the main environmental sink for this chemical. DEET has been detected in sewage treatment plant effluents, streams, surface water, and groundwater systems. The largest contribution for DEET in water systems comes from sewage effluents containing this chemical. Concentrations of DEET in effluents result from washing skin and clothing where commercial products containing DEET have been applied. Albeit a minor contribution, human absorption of DEET after application and subsequent excretion of DEET, and its metabolites, also contributes to effluent concentrations. DEET-contaminated effluents may also enter surface water and groundwater systems after passing through waste water treatment plants (WWTPs) or domestic septic systems. Additionally, recreational activities such as swimming, via swimmers with DEET products on their skin or clothing washing off, can contribute to DEET in water systems.

Studies have shown that DEET is not expected to bioconcentrate in aquatic systems. DEET is expected to be hydrolytically stable under environmental conditions. Little degradation is expected under anaerobic conditions; however, DEET is considered readily biodegradable in aerobic conditions and should not persist in the environment.

See Chapter 6 for more detailed information regarding concentrations of DEET in environmental media and its environmental fate.

The general population is exposed to DEET as a result of its use as an insect and acarid repellent intended for direct human application. Insect repellent products containing DEET range in concentration from 4 to 100%. As of March 2017, there were 27 companies in the United States that manufactured approximately 119 consumer products containing DEET. According to the U.S. EPA, as of February 2014, there were 123 active registrations for DEET, including co-formulations with other chemicals, formulations with sunscreen, and one registration for use on horses. Dermal application of repellents is the major route of exposure. Inhalation may be a route of exposure when aerosol formulations are used, albeit a minor route of exposure. Children are expected to be exposed to DEET by the same routes that affect adults. No data

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were located regarding DEET in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made. DEET absorbed through the skin, however, can transfer through the placenta and expose the fetus.

Data from the National Health and Nutrition Examination Survey (NHANES) show that levels of DEET in 74% of the study population were below the detection limits of 0.449 µg/L (1999–2000) and 0.1 µg/L (2001–2002) in the urine of 4,512 members of the U.S. general population sampled during these two surveys. The respective 90th and 95th percentile values were 0.11–0.13 and 0.13–0.22 µg/L. The highest levels were found in people 12–19 years old and in non-Hispanic whites. Levels of DEET for the survey years 2007–2010 were also below the detection limit (0.089 µg/L). It should be noted, that human monitoring data measuring the parent compound DEET does not directly correlate to initial exposure concentrations due to the fact that the majority of absorbed DEET is metabolized. The main metabolites of DEET in humans are 3-(diethylcarbamoyl) benzoic acid (DCBA) and N,N-diethyl-3-(hydroxymethyl) benzamide (DHMB). Data from NHANES for the years 2007–2010 show levels of both DCBA and DHMB in urine higher than those reported for the parent compound, DEET, indicating the relevance of their evaluation when assessing exposures to DEET. Details of the results can be found in Section 6.5.

2.2 SUMMARY OF HEALTH EFFECTS

Exposure of humans to DEET has been associated with a variety of health effects including neurological, respiratory, cardiovascular, gastrointestinal, dermal, and ocular. It should be noted, however, that considering the many millions of applications of DEET per year in the United States, there have been limited reports of serious health effects following DEET applications. A few deaths in humans have been associated with oral and dermal exposure to DEET, sometimes in combination with other drugs or chemicals. This also needs to be considered in studies reporting effects other than death since commercial DEET products usually contain additional ingredients. The most serious effects reported following oral and dermal exposure to products containing DEET have been neurological effects. Neurological signs and symptoms reported in children and adults include seizures, ataxia, restlessness, uncontrolled limb movements, agitation, aggressive behavior, combativeness, impaired cognitive functioning, and opisthotonos (a postural abnormality characterized by hyperextension of the back and neck muscles, with retraction of the head, and arching forward of the trunk). Because of the wide spectrum of neurological effects reported, some researchers have noted that it is unlikely that they were due to exposure to a single agent. In a study of 242 cases in the DEET Registry, a collection of self-reported cases spanning 6 years of DEET use in North America, there were 59 seizure cases. At the

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1-year follow-up of 35 of these cases, medical tests showed evidence of an underlying neurological disorder in five of these cases, questioning the role of DEET as the sole cause of seizures in those cases. The issue of seizures in children following exposure to DEET needs to be evaluated with caution. In the specific case of seizures, it should be noted that because a relatively high percentage (23–29%) of children are exposed to DEET in the United States and because seizure disorders occur in approximately 3–5% of children from any cause, it might be possible, just by chance alone, to erroneously find an association. There is no reliable information regarding doses or exposure concentrations associated with effects. A survey of 143 employees of the Everglades National Park, Florida who used DEET regularly in their work, showed that more highly exposed workers (estimated >4.25 g DEET/week or about 8.7 mg DEET/kg/day assuming 70 kg of body weight) had a higher prevalence of dizziness, disorientation, difficulty concentrating, and skin rashes than non-users of DEET. Because exposure was inferred from only survey responses, a notable weakness, the findings from this report should be interpreted with caution. In a study of 9,086 exposures involving insect repellents containing DEET reported to Poison Control Centers from 1985 to 1989, it appeared that the concentration of DEET in the product used was not related to the severity of the symptoms following exposure. Those patients experiencing a major effect had used products containing 11–50% DEET. The same observations were made in a later study of 20,764 exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997.

Exposure to DEET has produced skin irritation, desquamation of the skin, dermatitis, and erythema in humans. Cases of non-immunological and immunological contact urticaria have also been reported.

Neurological effects also have been reported in animals exposed to DEET primarily by the oral route or by application of DEET onto the skin. Results from high dose-studies in animals support the findings in humans exposed to high amounts of DEET. Tremors and seizures occurred at the highest oral doses tested: 400 mg DEET/kg/day in dogs and $\geq 2,000$ mg DEET/kg in rats. In rats, but not in dogs, the higher doses also caused histological alterations in the brain. Tremors were also reported in rats exposed by inhalation to a high concentration of 4,100 mg/m³ DEET aerosol. One study reported neurobehavioral alterations in rats acutely dosed by oral gavage with lower doses of DEET (500 mg/kg) but others have not. Dermal application of doses of 4 mg DEET/kg/day as 10 mg/mL DEET in 70% alcohol to a 2.5-cm² area for 60 days affected some sensory parameters in rats and doses ≥ 40 mg DEET/kg/day (which the authors considered equivalent to typical exposures of military personnel during wartime) induced histological alterations in various brain areas and affected cholinergic neurotransmitter systems. It should be mentioned, however, that some scientists have raised concerns about possible misinterpretation of the

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histopathological findings because of artifacts resulting from inadequate handling and fixation of the brain tissue. The neurobehavioral alterations reported in some of these studies, however, were not observed in a more recent similar study in rats that also applied doses of 40 mg DEET/kg/day, as 100 mg/mL DEET in 70% alcohol, to a larger 4-cm² exposure area and shorter 30-day exposure time. The apparent inconsistent results between some studies need to be resolved considering the differences in route of exposure, exposure area and exposure duration.

DEET exhibited relatively little systemic toxicity in repeated inhalation, oral and dermal exposure studies in animals. Daily intermittent exposure of rats to up to 1,511 mg/m³ aerosolized DEET (the highest concentration tested) for 13 weeks did not cause morphological alterations in organs and tissues or produce significant alterations in hematology or clinical chemistry tests. In general, alterations were seen only at the highest oral dose tested (≥ 400 mg DEET/kg/day). Oral studies reported reductions in body weight gain in rats, mice, hamsters, rabbits, and dogs. Oral exposure to DEET also caused alterations in serum electrolytes in hamsters, dogs, and rabbits. Other systemic effects induced by repeated oral exposure to DEET include slightly decreased hemoglobin and hematocrit, increased platelets, increased serum alkaline phosphatase, and decreased cholesterol in dogs, fatty changes in hepatocytes in rabbits, and increased cholesterol in rats. In the absence of histological alterations in organs and tissues, the toxicological significance of these findings is unclear. Following repeated dermal exposure, DEET was not a skin sensitizer in guinea pigs or rabbits, but induced erythema and acanthosis/hyperkeratosis in rats, skin desquamation, hyperkeratosis and acanthosis in micropigs and rats, and skin irritation in rabbits following repeated dermal exposure.

There are no studies of reproductive effects in humans exposed to DEET.

DEET did not affect fertility in male or female rats in a 2-generation continuous feeding study. DEET also did not induce gross or microscopic alterations in the reproductive organs of male rabbits, or male or female rats, mice, or dogs in intermediate- or chronic-duration oral studies, or in male rats in an intermediate-duration dermal study. DEET at ≥ 624 mg/kg/day, however, increased the incidence of tubular degeneration in the testes of hamsters in a 90-day study.

Exposure to DEET was not associated with developmental effects in two epidemiological studies. In one of them, pregnant women applied DEET onto themselves in the second and third trimester of pregnancy. The results did not show significant differences between exposed and control neonates regarding head and arm circumference or length or in a series of neurological tests in the neonates. The other

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epidemiological study did not find significant associations between the presence of DEET in maternal blood or cord serum and birth weight, head circumference, abdominal circumference, or birth length in neonates. DEET did not induce embryotoxicity or teratogenicity in rats or rabbits at doses that caused a significant reduction in maternal body weight gain during gestation. Sacrifices were conducted the last day of gestation in these studies. In the 2-generation continuous feeding study in rats, DEET induced significant reductions in weight in both male and female F1 and F2 pups during lactation.

Limited information exists regarding exposure to DEET and cancer and occupational exposure. A case-control study of testicular cancer and occupational exposure in Sweden reported a significant association between exposure to insect repellents for more than 115 days and testicular cancer. No evidence, however, was provided that DEET was the causative agent. In addition, exposure was assessed by self-recollection, which is known to be unreliable. DEET was not carcinogenic following long-term oral assays in rats, mice, or dogs or following long-term skin application to mice or rabbits. The EPA's OPP classified DEET as a Group D substance, not classifiable as a human carcinogen, based on no evidence of mutagenicity in multiple tests, or of carcinogenicity in long-term oral ingestion studies in adult rats or mice. DHHS and IARC have not classified DEET as to its carcinogenicity.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for DEET. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

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bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No inhalation MRLs were derived for DEET due to insufficient data. Qualitative information regarding effects in humans following inhalation exposure to DEET was found in a study of 20,764 exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997 (Bell et al. 2002). In 520 of these cases, inhalation was identified as the leading exposure route. Respiratory (coughing/choking, dyspnea, bronchospasm, respiratory depression, pneumonitis), cardiovascular (tachycardia, hypertension, hypotension), gastrointestinal (oral irritation, vomiting, nausea), and neurological (dizziness/vertigo, headache, drowsiness/lethargy) signs and symptoms were most commonly reported. About half of the subjects were reported or judged to suffer no ill effects due to DEET exposure. A similar percentage of subjects were reported or judged to have a minor effect. Four percent experienced a moderate or greater effect or a potentially toxic exposure. Similar qualitative data regarding 9,086 human exposures were published earlier by Veltri et al. (1994). In 2012, there were 4,075 single cases of exposure to insect repellents with DEET reported to the American Association of Poison Control Centers (AAPCC 2013). Two deaths were reported in this series of cases. Most of the other cases were in children ≤ 5 years of age ($n=2,316$, 57%) or adults ≥ 20 years of age ($n=829$, 20%), and the severity of health effects were primarily considered to be none ($n=576$, 14%) to minor ($n=1,176$, 29%). No information was provided regarding the remaining 57%. This qualitative information cannot be used for MRL derivation.

The animal data are restricted to only a few studies, some with significant limitations. Acute-duration inhalation studies have been conducted in rats and mice. Head-only exposure of rats to an aerosol of 85% DEET for 2–6 hours induced minor changes in the lungs and trachea, but no further details were provided (Ambrose 1959). The actual exposure concentration that animals received was not provided in this study and there was no indication that a control group was used. An additional acute-duration study in rats reported that 4-hour exposures conducted at concentrations of $\geq 2,300$ mg/m³ DEET aerosol decreased performance in behavioral tests conducted within 50 minutes of termination of exposure (Army 1979). Gross necropsy following a 14-day observation period did not show treatment-related lesions. The limited scope of the study and the lack of histological examination of tissues, particularly the nervous system, made this study inadequate for MRL derivation. Furthermore, the lowest concentration tested was considerably higher than a 4-hour LC₅₀ of 1,369 mg/m³ reported in mice (Deb et al. 2010). In a study

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in mice, head-only exposure to a target concentration of 135 mg/m³ DEET aerosol for 4 hours increased respiratory frequency, but this effect was not observed at lower or higher exposure concentrations (Deb et al. 2010). Other respiratory parameters that were measured were not affected. Because the actual exposure concentrations were not specified and, according to the investigators, were 50–60% of the target concentrations, the results of this study are unreliable.

Only a few intermediate-duration inhalation studies were available for review. In an early study by Ambrose (1959), exposure of rats to air saturated with vaporized DEET (approximately 71 mg/m³) 8 hour/day, 5 days/week for 7 weeks resulted in unspecified microscopic changes in the lungs and trachea. There was no indication that a control group was used in the study. Army (1980a) conducted 13-week intermittent exposure studies in Sprague-Dawley rats and Beagle dogs. In both studies, the animals were exposed whole-body to 252, 752, or 1,511 mg/m³ aerosolized DEET. End points examined in rats included body weight, gross and microscopic appearance of all major tissues and organs, hematology and clinical chemistry parameters, and oxygen consumption. No significant alterations were reported other than the transient appearance of a red exudate around the eyes and nose of rats exposed to 1,511 mg DEET/m³. The study in dogs tested only two animals per sex per exposure group and only evaluated hematology and clinical chemistry parameters as well as pulmonary function (compliance and resistance). No significant effects were reported. This information was inadequate for MRL derivation.

No chronic-duration inhalation studies in animals were located.

Oral MRLs

An acute-duration oral MRL for DEET was not derived. No reliable estimates of doses of DEET were available in the numerous cases of accidental or intentional ingestion of insect repellents containing DEET summarized in Chapter 3. The available acute-duration database in animals is limited. It should be noted that in all the acute-duration studies available for review, DEET was administered by gavage. Acute-duration studies provided information regarding lethal doses (Ambrose 1959; Carpenter et al. 1974; EPA 1998c; McCain et al. 1997; Verschoyle et al. 1992), developmental (Schoenig et al. 1994), and neurological (Schoenig et al. 1993, 1994; Verschoyle et al. 1992) effects in rats. In the developmental studies, the highest doses tested (750 mg/kg/day in rats and 325 mg/kg/day in rabbits) induced maternal toxicity in the form of significantly reduced body weight gain during the entire dosing period in rats (gestation days [GDs] 6–15) and during GDs 6–9 in rabbits and also induced adverse neurological signs in the rats (hypoactivity, ataxia, decreased muscle tone), although no incidence data

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were provided (Schoenig et al. 1994). These signs were opposite to what has been reported in humans who ingested high amounts of DEET (i.e., hyperactivity, tremors, seizures, restlessness, uncontrolled limb movements, agitation, and aggressive behavior) (Petrucci and Sardini 2000; Tenenbein 1987; Zadikoff 1979). The reasons for this are uncertain. No significant fetotoxicity or teratogenicity was observed in either species in this study, other than a 6% reduction in fetal weight in the high-dose rats that may have been related in part to the 35% reduction in maternal weight gain during the treatment period. A neurological study in rats reported that a single dose of 500 mg DEET/kg (the highest dose tested) delayed the response to a thermal stimulus and decreased vertical activity 1 hour after treatment but not at 24 hours or 14 days post-treatment (Schoenig et al. 1993). These effects were characterized in the study as slight and questionable by the investigators (Schoenig et al. 1993). Another neurological study reported that single doses of $\geq 1,000$ mg DEET/kg (approaching the lethal dose) induced clinical signs and histological alterations in the brain, but the exact dose level at which effects started to appear was not totally clear (Verschoyle et al. 1992). Although it would appear that studies such as the developmental study in rats and rabbits by Schoenig et al. (1994) or the neurotoxicity study by Schoenig et al. (1993) described above could be considered for MRL derivation, additional information suggests that it may not be appropriate to do so. Regarding the former, the Reregistration Eligibility Decision (RED) for DEET (EPA1998b) indicates that in an unpublished dose-range developmental toxicity study in rabbits administered DEET by gavage in doses ranging from 62.5 to 1,000 mg/kg/day on GDs 6–18, deaths occurred in groups dosed with ≥ 500 mg DEET/kg/day. Necropsy of the animals that died showed sloughing and/or ulceration of the stomach lining and suggested that the corrosive effects of DEET to the gastric lining may have been linked to the death of the rabbits. This effect was consistent with the report of significant reduction in maternal weight gain and food consumption during the dosing period in the developmental study in rabbits (Schoenig et al. 1994), as gastric irritation induced by DEET may have caused the animals to stop eating. This is also consistent with the results of a 15-day study in which rabbits dosed by gavage with 528 mg DEET/kg/day lost approximately 1/5 of their body weight during the study; no data regarding food consumption were provided in this study (Army 1980b). Also, in the 52-week study in dogs (Schoenig et al. 1999), tremors were observed in some dogs before administration of DEET in a capsule, and because of lack of temporal relationship, were not considered to be treatment-related. It is possible, however, that the dogs were able to associate feeding of a capsule with gastric discomfort, which may have caused the tremors. In the developmental study in rats (Schoenig et al. 1994), high-dose animals showed a significant reduction in weight gain and food consumption during dosing, although not as marked as the rabbits. In that study, two rats died on day 2 of treatment, but apparently no necropsy was conducted, so it is unknown whether gastric lesions occurred. Long-term dietary studies did not report gastrointestinal alterations in rats or mice administered doses of DEET

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comparable to those given in gavage studies (400–860 mg/kg/day to rats, 1,000 mg/kg/day to mice) (Ambrose 1959; Schoenig et al. 1999) and no other significant toxic effects were reported. Taken together, this information suggests that DEET given as a bolus dose may induce stomach irritation, which in turn may cause the animals to stop eating and, therefore, lose weight or gain less weight than untreated animals. This effect also suggests that decreases in body weight observed in animals following gavage administration of DEET may be secondary to gastric irritation and reduced food consumption and may not be appropriate as a basis for MRL derivation. Additionally, exposure to DEET by people living near hazardous waste sites would likely be through drinking water rather than by ingestion of a DEET bolus, as occurs with gavage dosing.

Schoenig et al. (1993) reported that rats treated with a single gavage dose of 500 mg DEET/kg showed delayed response to a thermal stimulus and decrease vertical activity and vertical time when tested 1 hour post-dosing. The toxicological significance of these alterations is unknown. Furthermore, the investigators noted that: *“The effects of the high-dose on the thermal response was weak inasmuch as the statistically significant effect was found only in an analysis that included both males and females in a factorial ANOVA, but fell short of significance even for the most affected sex, the females ($p < 0.06$) when the two sexes were analyzed separately.”* Since only vertical activity and vertical time were affected by treatment with DEET out of multiple activity parameters measured (horizontal activity, vertical activity, total distance travel, movement time, rest time, number of movements, vertical time, number of vertical movements, stereotype time, number of stereotypic movements, clockwise revolutions, and counterclockwise revolutions), confidence in an MRL based on this endpoint would be minimal at best. In conclusion, the available acute-duration oral database does not support derivation of an acute-duration oral MRL for DEET.

- An MRL of 1.0 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to DEET.

No relevant human data were located. Intermediate-duration oral studies provide information regarding systemic, neurological, reproductive, and developmental effects in various animal species, but failed to identify a sensitive target for DEET toxicity. The lowest lowest-observed-adverse-effect level (LOAEL) in any study was 25 mg DEET/kg/day for hyaline nephropathy in F1 males in a 2-generation continuous feeding study (EPA 1989). This hydrocarbon-induced nephropathy has only been demonstrated in adult male rats and has been associated to a specific protein, $\alpha_{2\mu}$ -globulin, which is produced under hormonal control by the liver (Alden 1986; Swenberg 1993). However, the $\alpha_{2\mu}$ -globulin is unique to male rats and is not present in human kidneys. Hence, this particular nephropathy has no significance for humans and

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would therefore be inappropriate to use for MRL derivation. Significantly higher LOAELs were reported in other intermediate-duration oral studies. A 200-day feeding study in rats reported a no-observed-adverse-effect level (NOAEL) of 863 mg DEET/kg/day (the highest dose tested) for organ histopathology and a LOAEL of 863 mg/kg/day for a statistically significant reduction (11.1%) in final body weight in female rats; food consumption was not significantly affected in this study and no clinical signs were observed (Ambrose 1959). A 90-day feeding study in hamsters reported NOAELs of 940 mg DEET/kg/day (which was also the highest dose tested) for organ histopathology (EPA 1990b). That study also identified a LOAEL of 624 mg DEET/kg/day for approximately 13% reduction in final body weight in male hamsters and for histopathology of the testes, and a LOAEL of 940 mg DEET/kg/day for a 10–16% increase in serum potassium in both male and female hamsters. Feeding dogs with DEET through a capsule for 52 weeks resulted in LOAELs of 400 mg DEET/kg/day for statistically significant hematology changes in females (reduced hemoglobin at 6 months, reduced hematocrit at 12 months, increased platelets at 6 and 12 months) and clinical chemistry changes in males (decreased serum alkaline phosphatase at 6 months, reduced cholesterol at 6 and 12 months, increased serum potassium at 6 months) (Schoenig et al. 1999); histological examination of tissues and organs was unremarkable. The toxicological significance of these effects is unknown, particularly since they were observed in one sex or the other. Terminal body weight was also reduced in dogs fed 400 mg DEET/kg/day. Although the extent cannot be read from a graph in the paper, the investigators noted that body weight decreased at several time points during the study for both males and females. Dogs in these groups consumed less food during the initial weeks of the study, which may have caused these animals growth to lag behind for the rest of the study. The authors stated that the absolute weight differences were generally small, within a few grams, and considered that 1,000 mg/kg/day was the only dose at which body weight and food consumption differences were toxicologically relevant. Treatment-related tremors and ataxia were also reported in one out of eight dogs several times after dosing with 400 mg DEET/kg/day. A 15-day gavage study in male rabbits reported LOAELs of 528 mg DEET/kg/day (highest dose tested) for a 14% decrease in serum calcium and 22% body weight loss (starting weight approximately 3,500 g, terminal weight approximately 2,750 g) (Army 1980b). No information was provided regarding food consumption. Histological examination of organs and tissues showed fatty changes in hepatocytes, but no significant alterations in other organs or tissues. The possible role that the considerable weight loss in high-dose rabbits in a short period of time could have had in the other effects reported was not discussed in the study. A study that conducted neurological examinations of F2 rats that were exposed to DEET during gestation, lactation, and then directly for approximately 9 months reported a transient increase in motor activity at 500 mg DEET/kg/day during the first 5–15 minutes of testing. No such increase was seen during the remaining 40 minutes of the test session (Schoenig et al. 1993). The investigators considered

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this effect of minor or questionable significance based on the small magnitude of the changes and the transient nature (Schoenig et al. 1993). This study also reported a reduction of approximately 14% in final body weight in high-dose males, but no data on food consumption were provided. The lowest LOAEL in the database other than the 25 mg DEET/kg/day for hyaline nephropathy mentioned above, was 250 mg DEET/kg/day (highest dose tested) for significantly ($p < 0.01$) reduced (11–13.3%) body weight in F1 and F2 male and female rat pups on lactation days 14 and 21 in the 2-generation continuous feeding study (EPA 1989). The NOAEL in the study was 100 mg DEET/kg/day. Because the effects showed dose-response relationships, occurred in both male and female pups, were observed in two generations, and may have resulted in important developmental delays, the 2-generation continuous feeding study in rats was selected for derivation of an intermediate-duration oral MRL for DEET. A detailed summary of the EPA study (1989) is presented in Appendix A.

Data for body weight in F1 and F2 male and female rat pups on day 21 of lactation in the EPA study (1989) could not be analyzed using the benchmark dose (BMD) approach for the following reason. While the total number of F1 and F2 pups alive on lactation day 21 is provided in the EPA study (1989), the sex distribution is not; however, the table that shows the body weight of the F1 and F2 pups presents the body weight broken down by sex. Without knowing the number of animals examined (n), the BMD approach could not be used. Therefore, the NOAEL/LOAEL approach was used for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the NOAEL of 100 mg DEET/kg/day results in an intermediate-duration oral MRL of 1 mg/kg/day for DEET.

A chronic-duration oral MRL was not derived for DEET. No relevant human data were located. Well-conducted chronic dietary studies in rats and mice found virtually no DEET toxicity at the highest doses tested: 400 mg DEET/kg/day for 104 weeks in rats and 1,000 mg DEET/kg/day for 78 weeks in mice (Schoenig et al. 1999). This study conducted gross and microscopic examination of all major organs and tissues and hematological tests; in addition, ophthalmologic and clinical chemistry tests were conducted in rats. There were no treatment-related clinical signs during the studies. The only significant effects reported were an increase in serum cholesterol and reduced body weight in high-dose female rats and in high-dose mice. The reductions in body weight appeared to be associated with reduced food consumption, but no data were shown. The toxicological significance of the increase in serum cholesterol in female rats was unknown; in the same study, male dogs were dosed with 400 mg DEET/kg/day in a capsule for 52 weeks experienced a decrease in serum cholesterol. The available chronic-duration oral database does not support derivation of a chronic-duration oral MRL for DEET. Long-term exposure,

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however, does not lead to more toxic effects than those reported for intermediate-duration exposure. The intermediate-duration oral MRL of 1 mg/kg/day for DEET, therefore, is considered protective for chronic-duration exposure.