CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DEET

Chemical Code # 000189, Tolerance # 50191
SB 950 # 102

September 23, 1987
Revised 8/30/91, 1/24/92, 7/15/92, 9/24/93, 3/30/95, 6/12/96, 7/12/96, 9/26/97, 4/26/99, 6/18/99, 6/21/99

I. DATA GAP STATUS

Combined, rat (chronic/onco):	No data gap, no adverse effect.
Chronic, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratogenicity, rat:	No data gap, no adverse effect
Teratogenicity, rabbit:	No data gap, possible adverse effect.
Gene mutation:	No data gap, no adverse effect
Chromosomal aberration:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No study required at this time

Note, Toxicology one-liners are attached

All volume/record numbers through 215/154697 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T990426
Revised by: M. Silva 8/30/91, 1/24/92, 7/15/92, 9/24/93, 3/30/95, 6/12/96, 7/12/96, 9/26/97, 4/26/99; J. Gee, 6/18/99; M. Silva, 6/21/99.

THESE PAGES CONTAIN SUMMARIES ONLY. EACH INDIVIDUAL WORKSHEET MAY CONTAIN ADDITIONAL EFFECTS.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

Subchronic Studies:

171 132318 "Evaluation of DEET in a Multistrain 90-Day Dietary Renal Toxicity Study in Rats," (Goldenthal, E.I., IRDC, Mattawan MI; Laboratory ID#: 555-022, 10/14/92). DEET technical (98.301% pure) was fed in diet to CD, Fischer and NBR male rats (10/strain/dose) at 0 and 400 mg/kg for 90 days in order to assess renal effects. A NOEL was not achieved in this study and there is a possible adverse effect: Histopathology in the renal tubules showed the presence of hyaline droplets, regenerative tubules, chronic inflammation and granular casts. Data show that the renal toxicity seen in male rats treated with DEET is due to excessive accumulation of a-2u-globulin in the cells lining the renal tubules. This effect occurred in CD and Fischer 344, but not in NBR rats. These data are supplemental. M. Silva, 3/21/95.

169 132316 "Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Castrated Male Rats," (Goldenthal, E.I., IRDC, Mattawan MI; Laboratory ID#: 555-010, 8/9/89). DEET technical (98.301% pure) was applied dermally (unoccluded) to the shaved skin of Charles River CD male rats (15/sex/dose) at 0 (vehicle = tap water) - castrated, 1000 mg/kg (both castrated and uncastrated) - limit test, 5 days/week for 13 weeks. There was not a NOEL in this study, since only the limit test was used (1000 mg/kg). At 1000 mg/kg, both castrated and non-castrated rats had decreased bodyweights and slight erythema at the application site. Castrated, treated rats had decreased absolute and relative kidney weights. **Possible adverse effect:** Castrated and non-castrated treated rats showed renal tubular histopathology (hyaline casts & droplets, inflammation, regeneration, granular casts and positive stains for the presence of a-2u-globulin) that were associated with DEET. These data are supplemental. M. Silva, 3/20/95.

112 098122 "Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Rats," (Johnson, D.E., International Research and Development Corporation, MI, 6/5/87). DEET technical (purity = 98.301%; LOT #: A-1-96) was administered dermally to Charles River CD rats (15/sex/dose) at 0 (tap water at 1000 mg/kg), 100, 300 and 1000 mg/kg (5 days/week) for 13 weeks. LOEL = 100 mg/kg (Red and scabbed areas were observed in both sexes at all doses at the application site (macroscopic scales and microscopic acanthosis and hyperkeratosis) in almost all treated animals. Both sexes at 1000 mg/kg showed significant decrease in body weight gain. Males showed enlarged kidneys in a dose-related manner at all doses, accompanied at $\geq$ 300 mg/kg by increased urea nitrogen; decreased glucose at 1000 mg/kg, increased absolute and relative kidney weights and granular casts, inflammation, regeneration and hyaline droplets at $\geq$ 100 mg/kg. Females showed increased relative kidney weights and very slight pathology in kidneys at 1000 mg/kg.) **Possible adverse effect (dermal irritation).** These data are supplementary. M. Silva, 7/12/96.

111 098121 "Evaluation of DEET in a 90-Day Oral Dose Range Finding Study on Rats," (Johnson,

D.E., IRDC Project ID #: 555-001, 6/1/87). DEET technical (98.301% pure, IRDC ID#: 8812B) was offered in the diet to Charles River CD Rats (15/sex/dose) at 0 (diet), 100, 500, 1000, 2000 and 4000 mg/kg/day for 90 days. Due to body weight depression and mortality during week 1, rats at 4000 mg/kg were offered control diet beginning week 2 and were sacrificed week 3 (no analysis of these animals). LEL = 100 mg/kg (Clinical signs in both sexes showed firm areas on ventral abdomen, hunched posture, high carriage in locomotion at 2000 mg/kg. Decreased defecation--males at ≥ 2000 mg/kg, females at ≥ 1000 mg/kg was also noted. Males showed cool to touch, reduced motor activity, labored breathing, tail raised, moribund, and eye partially closed at 2000 mg/kg. Body weights in both sexes were significantly reduced at ≥ 2000 mg/kg. Lymphocytes in males were significantly decreased at ≥ 1000 mg/kg. Females showed significantly increased erythrocytes, hematocrit, mean cell volume (2000 mg/kg) and mean cell hemoglobin (≥ 1000 mg/kg). Absolute brain weight was decreased in males at 2000 mg/kg, and relative brain/body weight was increased at ≥ 500 mg/kg in both sexes. Liver weight was significantly increased at all doses in males and at ≥ 500 mg/kg in females. Relative liver/body weights were increased in both sexes at ≥ 500 mg/kg; liver/brain weights were increased in females at ≥ 500 mg/kg. Kidney weights were significantly decreased at 2000 mg/kg in males and ≥ 1000 mg/kg in females. Kidney/body weights were increased at ≥ 500 mg/kg in males. Kidney/brain weight was significantly decreased in males at 2000 mg/kg and in females at ≥ 1000 mg/kg. Testes/body weight was increased at ≥ 1000 mg/kg. Ovary and ovary/brain weights were decreased at 2000 mg/kg. Histopathologically, males showed granular casts, inflammation, regeneration and hyaline droplets at all doses.) These data are supplementary. M. Silva, 8/30/91.

Combined (chronic and oncogenicity):

** 176 133986 "Evaluation of DEET in a Two-Year Dietary Toxicity and Oncogenicity Study in Rats," (Goldenthal, E.I., IRDC, Mattawan MI; Laboratory ID#: 555-023, 1/3/95). DEET technical (98.301% pure) was fed in diet to Charles River CD rats (60/sex/dose) at 0 (controls 1 & 2), 10, 30 and 100 mg/kg (males) and 0 (controls 1 & 2), 30, 100 and 400 mg/kg (females) for 2 years. Chronic NOEL = 100 mg/kg (Females showed significant decrease in bodyweight and food consumption at 400 mg/kg. Cholesterol was increased in females at 400 mg/kg throughout the study. Females at 400 mg/kg had decreased relative (to bodyweight) liver weight.) Males did not show significant effects in this study. There were no oncogenic effects induced in rats by DEET in this study. No adverse effects. ACCEPTABLE. M. Silva, 3/21/95.

CHRONIC, DOG

Subchronic Studies:

177 134315 "Evaluation of DEET in an Eight Week Oral Gelatin Capsule Toxicity Study in Dogs," (Goldenthal, E.I., IRDC, Mattawan MI; Laboratory ID#: 555-027, 1/3/95). DEET technical (98.301% pure) was fed in gelatin capsules to Beagle dogs (2/sex/dose) at 0 (gelatin capsule + white mineral oil), 50, 100, 200 and 400 mg/kg for 8 weeks. Dosing was divided into am & pm administrations following a 1 hour feeding period. NOEL = 100 mg/kg (Ptyalism in both sexes was observed with increased degree at ≥ 200 mg/kg. Both sexes at ≥ 200 mg/kg had emesis (dose related increase). Relaxed nictitating membrane was also observed at ≥ 200 mg/kg, primarily in males. Bodyweights and food consumption were decreased at 400 mg/kg in both sexes. Serum cholesterol was slightly decreased in males at 400 mg/kg. Absolute weights of testis/epididymis in males were decreased

at 400 mg/kg.) No adverse effect. These data are supplemental. M. Silva, 3/23/95.

178 134316 "Evaluation of DEET in an Eight Week Dietary Toxicity Study in Dogs," (Goldenthal, E.I., IRDC, Mattawan MI; Laboratory ID#: 555-020, 1/3/95). DEET technical (98.301% pure) was fed in diet to Beagle dogs (2/sex/dose) at 0, 300, 1000, 3000 and 3000/4500/6000 ppm for 8 weeks. High dose dogs were initially offered 6000 ppm DEET for the first 15 days on study, 4500 ppm weeks 4 and 5 and 3000 ppm during weeks 7 and 8. Basal diet was offered weeks 3 and 6. NOEL = 3000 ppm (Clinical signs (thinness & decreased activity), decreased bodyweights, food consumption, absolute weights of liver/gallbladder, heart and kidneys were observed at the high dose (3000/4500/6000 ppm). The absolute spleen weights for high dose males were decreased. Brain/bodyweight and liver/bodyweight ratios in both sexes of high dose dogs were increased. At the high dose, cytoplasmic vacuolization of the cortical kidney tubules (1/2 M & 2/2 F), hypocellularity of rib bone marrow (2/2 M & 2/2 F) and thymic atrophy and hemorrhage (1/2 M & 2/2 F) occurred.) No adverse effect. These data are supplemental. M. Silva, 3/22/95.

Chronic Study:

** 164 131265 "Evaluation of DEET in a One-Year Chronic Oral Toxicity Study in Dogs," (Goldenthal, E.I., IRDC, Mattawan MI; Laboratory ID#: 555-021, 6/30/94). DEET technical (98.301% pure) was fed in gelatin capsules to Beagle dogs (4/sex/dose) at 0 (gelatin capsule + white mineral oil), 30, 100 and 400 mg/kg for 1 year. Dosing was divided into am & pm administrations following a 1 hour feeding period. NOEL = 100 mg/kg (At 400 mg/kg: Both sexes showed an increased emesis along with ptyalism. Ataxia, tremors, abnormal head movements and convulsions were observed in 1 male (#3597) throughout the study (30 min. post-dosing). Both sexes showed $\geq$ 10% lower body weight through week 26 and had lower food consumption (weeks 1-3, males and week 2, females). Both sexes had decreased hematocrit and hemoglobin at 6 and 12 month analyses. Females showed an increase in platelet counts at 6 and 12 months. Alkaline phosphatase was increased in males at the 6 and 12 months. Males had decreased cholesterol at 6 and 12 months and females had decreased cholesterol at 6 months. Physical examination showed 3/4 females were thin at terminal sacrifice. Brown pigment in the mandibular lymph node was observed in males and uterine hyperplasia and mononuclear infusion was observed in females.) No adverse effect. ACCEPTABLE. M. Silva, 3/28/95.

156 128426 This volume contains a discussion of the possibility that the tremors observed in 2/8 dogs at 100 mg/kg were a treatment-related adverse effect. M. Silva, 3/30/95.

ONCOGENICITY, MOUSE

Subchronic Study:

143 118053 "Evaluation of DEET in a 90-Day Oral Dose Range Finding Study in Mice," (Johnson, D.E., International Research and Development Corporation, Mattawan, MI; June 2, 1987; Report #: IRDC 555-002). DEET technical (98.31% pure) was fed in diet to Charles River CD-1 mice at 0, 300, 1000, 3000, 6000 and 10000 mg/kg/day for 90 days (Mice at 10000 mg/kg/day were removed from treatment and put on control diet on study day 5. At 6000 mg/kg/day, mice rejected diet during weeks 1-2. In both these groups, animals were sacrificed and discarded week 3.) NOEL < 300 mg/kg (Effects were observed at all doses. Clinical effects were observed in both sexes at $\geq$

3000 mg/kg/day. Body weights and food consumption were significantly decreased at ≥ 3000 mg/kg/day. Both sexes showed liver pathology (accentuated lobulation & diffuse, multilobar mottling), accompanied by histology (hypertrophy), along with erosions in the stomach mucosa at 3000 mg/kg/day. Both sexes showed significantly increased liver weights at 3000 mg/kg/day. Significantly increased absolute (both sexes) and relative (males) liver weights occurred at ≥ 1000 mg/kg/day. Females showed increased relative liver weights at all doses and decreased brain weights at 3000 mg/kg/day.) This study is a supplemental range-finding study. M. Silva, 9/20/93.

116 111041 This volume contains the same study as 143 118053, but without the individual data. M. Silva, 9/24/93.

Oncogenicity Study:

** 081, 116 090994, 111041 "Evaluation of DEET in an Eighteen Month Dietary Oncogenicity Study in Mice", (E. I. Goldenthal, International Research and Development Corporation, Laboratory Project ID 555-005, January 8, 1990). DEET, purity 100%, was administered in the feed at concentrations of 250, 500 or 1000 mg/kg to 60 Charles River CD-1* mice/sex/group for 78 weeks. This study also includes a control group (feed only). The possibility of adverse effects could not be evaluated, due to the lack of an MTD. Previously reviewed as unacceptable (Silva, 5/24/91), upon receipt and review of a range-finding study, this study has been upgraded to acceptable. NOTE: A separate review was performed on the range-finding study (116 111041--worksheet included, M. Silva, 1/10/92). The study has subsequently been re-evaluated and a NOEL of 500 mg/kg has been determined based on a significant increase in hyperplastic nodules of the liver in both sexes at 1000 mg/kg when compared to control group 2 (but not group 1), an increase in bile duct hyperplasia in males (significant by trend analysis but not pair-wise comparison) and a significant increase in absolute and relative liver weights were observed in both sexes at 1000 mg/kg. The study status is unchanged, except a NOEL of 500 mg/kg is concluded, based on liver observations. No adverse effect. M. Silva, 4/27/99.

024 17803, "Testing of Cosmetics, Ingredients of Sunscreen Ointments, Insect Repellents, and Detergents on Skin of Mice and Rabbits: Lifespan Studies," (Eppley Institute, Omaha, Nebraska, 10/1/76). DEET (no purity information) applied to flank skin of 50 female Swiss mice/group or 5 female New Zealand rabbits/sex/group; 10%, 50% or 100% solutions in 0.2 ml acetone twice weekly for life. No adverse effects indicated**:** No tumors observed in rabbits and no treatment-related tumors in mice. UNACCEPTABLE not upgradeable. Only one sex treated, treatment regimen not justified, and insufficient information presented for independent evaluation. (NLH/ C. Aldous, 9/11/87).

004 926115 Journal article summarizing 024 17803.

016 003240 Summary in EPA registration standard of 024 17803.

SUBCHRONIC, MICROPIG

168 132315 "Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Micropigs," (Goldenthal, E.I., IRDC, Mattawan MI; Laboratory ID#: 555-018, 8/15/91). DEET technical (98.301% pure) was applied dermally (unoccluded) to the shaved skin of micropigs (4/sex/dose) at

0 (vehicle = tap water), 100, 300 and 1000 mg/kg (limit test), 5 days/week for 13 weeks. NOEL < 100 mg/kg (There was a dose-related increase in desquamation, dry skin and abrasion at all doses, which decreased in time of onset and increased in severity, with dose. Acanthosis, ulcer, subacute inflammation and epidermal exudate were observed in males at ≥ 300 mg/kg and in females at 1000 mg/kg. Hyperkeratosis was observed in both sexes at all doses.) **No adverse effect.** These data are supplemental. M. Silva, 3/15/95.

SUBCHRONIC, HAMSTER

170 132317 "Evaluation of DEET in a 90-Day Dose Range Finding Study in Hamsters," (Goldenthal, E.I., IRDC, Mattawan, MI; Laboratory Project ID #: 555-012, 10/25/89). DEET technical (98.301% pure) was fed in diet to Golden Syrian VAF/Plus hamsters (15/sex/dose) at 0, 1000, 5000, 10000, 15000 ppm for 90 days. NOEL = 1000 ppm (There were increased deaths in both sexes at 15000 ppm. Clinical signs were observed at ≥ 5000 ppm. Bodyweights in males at ≥ 5000 ppm and in females at ≥ 10000 ppm were significantly decreased. Food consumption was significantly decreased in both sexes at 15000 ppm. Males showed macroscopically smaller testes and epididymides at ≥ 10000 ppm and females at 15000 ppm had increased stomach erosion. Both sexes had increased brain/bodyweight % at ≥ 10000 ppm. Males showed increased kidney/bodyweights % at ≥ 10000 ppm and increased liver/bodyweight % at 15000 ppm. **Possible adverse effect:** A significant decrease in testis weights were observed at ≥ 10000 ppm. Males had testicular tubular degeneration and smaller epididymides with luminal cellular debris at ≥ 10000 ppm.) These data are supplemental. M. Silva, 3/14/95.

REPRODUCTION, RAT

** 083 090996, "Evaluation of DEET in a Two Generation Reproduction/Fertility Study in Rats", (J. L. Schardein, International Research and Development Corporation, Laboratory Project I.D. IRDC 555-004, 1/23/89). DEET (purity = 98.3%, LOT: A-1-96) was administered in the feed at concentrations of 0 (diet only), 500, 2000 and 5000 ppm to 28 Charles River CD* rats/sex/group. Treatment period was for 80-93 days prior to mating and continued to scheduled sacrifice of F0 or F1 parents. Reproduction NOEL > 5000 ppm (No reproduction effects were reported at any level). When originally review, the Subchronic Parental NOEL was 2000 ppm (Silva, 6/4/91). Upon re-evaluation of F0 male body weights (Silva, 6/11/96) the NOEL has been lowered to 500 ppm (Body weight was statistically lower during the study at ≥ 2000 ppm in F0 males, and in both sexes of F1 adults at 5000 ppm. The presence of hyaline droplets, chronic inflammation, regenerative tubules and granular casts was increased in the kidneys of F1 adult males (alpha 2u globulin nephropathy).) Pup NOEL = 2000 ppm (Body weights were significantly decreased in both generations of pups from day 7-21 of lactation.) The study was recently re-evaluated and the 6% bodyweight decrease in F0 males at 2000 ppm was considered insufficient to lower the NOEL to 500 ppm. Therefore, the Parental NOEL = 2000 ppm as stated in the original review. ACCEPTABLE. No adverse effect. (Silva, 6/15/99).

215 154697 This volume contains a discussion of the body weight effects observed in studies 083

090996, the rat reproduction study and study 118 112057, the rat neurotoxicity study. No worksheet. M. Silva, 9/24/97.

006 926116, "The Effect of DEET (N,N-Diethyl Toluamide) on the Morphology, Viability and Count of Sperm in Rats Exposed by Dermal Administration", (Litton Bionetics, Kensington, Maryland, Project No. 21124, 9/25/80). DEET (98.3% meta isomer) was applied to skin at 0, 100, 300 or 1000 mg/kg. No adverse effects were noted in parameters studied: sperm number, viability, and morphology. This ancillary reproduction study provides limited information about effects on male reproduction. (Cannot be "upgraded" to fill reproduction effects data requirement). (NLH/ C. Aldous, 9/14/87).

012 926119, "Evaluation of DEET (N,N-Diethyltoluamide) in the Spermhead Abnormality Assay," (Litton Bionetics, Kensington, MD, 9/79). N,N-Diethyltoluamide (no purity information) at 0, 250 750 & 1500 mg/m^3 by inhalation for 6 hours/day, 5 days/week for 13 weeks; sperm analyzed for morphology; 10 animals/group; **Possible adverse effect**: increased percentage of abnormal sperm (signif. by t-test for 1500 mg/m^3 group, but ANOVA for all groups was not significant). Limited information for independent adverse effects assessment; Ancillary reproduction study only, not upgradeable" (No additional information required of this study). (J. Remsen 4/18/85, review indicated "Insufficient information for evaluation". Re-examined by NLH/C. Aldous on 9/14/87, considering also 024:17801, and "**Possible adverse effect**" noted in second review.)

024 017801 Critique of 012:926119 report interpretations by R. A. Sherman, who noted that negative ANOVA precludes valid use of "t" test for evaluation of controls vs high dose group. Correlation coefficient also not significant. Other weaknesses of study were noted. (J. Remsen (Gee), 4/18/85 and NLH/ C. Aldous, 9/14/87)

016 061104 "Toxicology Profile, Technical Deet, Reproduction (Sperm Abnormality)," Gleiberman et. al., 1976, Summary in EPA registration standard; **Possible adverse effect indicated, however insufficient information for EPA evaluation**: Sperm abnormality (sperm motility time and pathological forms); UNACCEPTABLE - Very Brief Summary of a study EPA judged to be inadequate due to insufficient information and lack of characterization of the test chemical. (One-liner only, no worksheet). (NLH/ C. Aldous, 9/14/87).

024 017804-5 "A Study of the Remote Consequences of the Use of Repellents. Communication I. An Experimental Study of the Consequences of the Long-Term Action of the Repellent Diethyltoluamide (DET)," ed. Parazitol. Parazit. Bolezni 45 (1), 65-69 (1976), from the All-Union Scientific-Research Institute of Disinfection and Sterilization, Moscow; DET (no purity information, but of "domestic manufacture") applied 5 times/week for 6 months or 1 - 1.5 months to male or female white mongrel rats, animals subsequently mated; 12 females & 6 males/group. **Possible adverse effects indicated:** increased implantation losses, fetal death and neonatal mortality, reduced fertility in treated females group; reduced fertility, increased post-implantation death and delayed neonatal development in the treated male group. NOEL < 100 mg/kg; Incomplete, UNACCEPTABLE - Not upgradeable (too few animals per group, unacceptable protocol). (J. Remsen (Gee), 4/18/85).

CONCLUSION: In studies 926119 (inhalation), 061104 and 017804 there were indications of adverse effects relating to reproduction. Each of these studies was flawed and unacceptable. The

test chemical in the two dietary studies was not characterized and therefore, it is not known what the animals were treated with. The inhalation study was not acceptable but inhalation is not a primary route of exposure for DEET. No adverse effects for reproduction or development were observed in the most recent, and acceptable study (090996). Nor were adverse effects observed in 926116, a dermal exposure study (primary route of exposure). Therefore, DEET, administered in diet is not considered to induce adverse effects for reproduction in rats. (M. Silva, 7/16/91)

TERATOGENICITY, RAT

** 082 090995, "Developmental Toxicity Evaluation of DEET Administered by Gavage to CD* (Sprague-Dawley) Rats", (T. L. Neeper-Bradley, Bushy Run Research Center, Export, PA., Laboratory Project I.D. 52-603, 1/4/90). DEET, purity = 98.3% was administered by gavage at concentrations of 125, 250, or 750 mg/kg/day to 25 mated Sprague-Dawley rats/group on gestation days 6 through 15 (gestation day 0 = the presence of a copulation plug). The controls received Mazola* corn oil by gavage. Maternal NOEL **=** 250 mg/kg/day (Decreased body weight gain and food consumption; hypoactivity, ataxia, decreased muscle tone; increased liver weight at 750 mg/kg/day).Developmental NOEL **=** 250 mg/kg/day (Significant reduction in fetal weight). ACCEPTABLE. (Kishiyama & Silva, 5/28/91)

024 017799 "An Investigation of the Embryotoxic Properties of the Repellent Diethyltoluamide," (Farmakol. Toksikol. 38(2), 202-205 (1975), from the All-Union Scientific-Research Institute of Disinfection and Sterilization, Moscow); 100 or 1000 mg/kg "DETA" (purity not stated) applied to skin (approx. 30 cm^2) of rats (strain not specified) daily from day one of mating; 20 rats/level but half sacrificed day 19 and half allowed to give birth. **Possible adverse effects indicated**: increased resorptions, decrease in neonatal weight gain, delayed neonatal development, dose-related increase in neonatal deaths. NOEL < 100 mg/kg; Incomplete, UNACCEPTABLE - Not upgradeable (too few animals/group, only 2 dose levels). (J. Remsen (Gee), 4/18/85).

006 926114 "Effect of `MGK Diethyltoluamide' on the Embryonic Development of Rats After Oral Application," (International Bio-Research, Inc., 2/77). `MGK Diethyltoluamide' (no purity information). 0, 7.9, 19.94 or 79.76 mg/kg (0, 8, 20 or 80 ul/kg) by gavage in peanut oil (note that treatment began on day 5 of gestation). **Possible adverse effect**: apparent maternal and developmental toxicity NOEL = 20 ul/kg (approx. 19.9 mg/kg), based on increased incidence of total litter losses and decreased implantation rate. Incomplete, UNACCEPTABLE - Unlikely to be upgradeable: (dose levels not justified, and no clear evidence of maternal toxicity; route of exposure may not have been the most appropriate; EPA has classified this study as "supplementary data"; other deficiencies in Section IV of review). (NLH/C. Aldous, 9/15/87).

004 926113 (Partial duplicate of 006:926114)

CONCLUSION: Two studies showed indications of adverse effects for development but both studies were flawed and unacceptable. One study (dermal) used very high doses and the other study (gavage) used peanut oil as a vehicle for DEET. In both studies, the purity of the test material was not characterized. The most recent study (acceptable, according to current FIFRA Guidelines) showed no adverse effects for development or teratogenicity. In this study, corn oil was used as a vehicle and doses went to 750 mg/kg/day. Therefore, based primarily on the most

recent (acceptable) study, DEET is not considered to induce adverse effects for teratology in rats. (M. Silva, 7/20/91)

TERATOGENICITY, RABBIT

Rangefinding Study:

124 114611 "Developmental Toxicity Dose Range-Finding Study of DEET Administered by Gavage to New Zealand White Rabbits," (Neeper-Bradley, T.L., Bushy Run Research Center, Union Carbide Chemicals and Plastics Company, Inc., 5/1/92.) DEET technical (98.69% pure) was administered by gavage (undiluted) to timed-pregnant New Zealand White rabbits at 0.0625, 0.125, 0.250, 0.50 and 1.0 g/kg/day (limit test) or 0 (corn oil) during days 6-18 of gestation (5/sex/group). Animals were sacrificed of gestation day 29. **Maternal NOEL =** 0.25 g/kg (Mortality was increased and there was a transitory decrease in body weight gain and food consumption at ≥ 0.5 g/kg. Clinical signs showed an increase in rapid respiration (≥ 0.25 g/kg), hypoactivity and ataxia at 1.0 g/kg.) **Developmental NOEL**: There were no significant effects at any dose. **No adverse developmental effects.** The study is considered supplemental. M. Silva, 7/7/92.

Definitive Studies:

028, 113 035490, 093223 "Effect of Dermal Applications of N,N-Diethyl-meta-toluamide (M-MET) on the Embryonic Development of Rabbits," (Angerhofer, R.A. and Weeks, M.H., United States Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD, 7/80). N,N-Diethyl-meta-toluamide (m-Det, DEET, DETA; minimum meta isomer content of 95% and 5% maximum of other isomers; lot #: 7141) was administered dermally to mated New Zealand White rabbits (20/dose) at 0 (untreated), EtOH (vehicle control), 50, 100, 500 and 1000 mg/kg during days 1-29 of gestation on skin areas of up to 150 cm2 (non-occlusive). NOEL < 50 mg/kg (Dermal effects were observed throughout the study. Significant decrease in food consumption days 1-15 at ≥ 500 mg/kg. Death was reported in 6/20 rabbits at 1000 mg/kg.) Originally reviewed as unacceptable (Remsen, 10/4/85), upon submission of individual data, the study remains unacceptable and is not upgradeable. The deficiencies are too numerous and detract in critical ways from interpreting the data. M. Silva, 1/10/92.

**** 119, 124 112060, 114612** "Developmental Toxicity Evaluation of DEET Administered by Gavage to New Zealand White Rabbits," (Chun, J.S. and Neeper-Bradley, T.L., DEET Joint Venture/Chemical Specialties Manufacturers Association, Union Carbide, Bushy Run Research Center, 12/6/1991). DEET (N,N'-diethyl-m-toluamide, 98.69% pure) was administered by gavage to mated New Zealand White rabbits (16/dose) at 0 (corn oil), 30, 100 or 325 mg/kg (undiluted DEET) days 6-18 of gestation. **Maternal NOEL** = 100 mg/kg (Transitional decrease in food consumption and body weight gain at 325 mg/kg.) **Possible adverse effect. Developmental NOEL** = 30 mg/kg (Thoracic centra #6 poorly ossified was increased in litters and fetuses at 100 mg/kg (at 325 mg/kg also, but not over historical controls). Extra rib #13 (unilateral) and sternebra #6 split were increased at 325 mg/kg in fetuses and litters. Sternebra #5 unossified was increased in both litters and fetuses at 325 mg/kg.) This study was originally reviewed as unacceptable (M. Silva, 1/17/92). Upon submission and review of the requested information (The dose-rangefinding study (BRRC Report #: 54-580; DPR 124/114611), historical controls for skeletal variations in New

Zealand White and actual volume of DEET administered/dam during the study (DPR 124/114612), the study has been upgraded to acceptable status. M. Silva, 7/8/92.

GENE MUTATION

** 084 090997, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay", (R.H.C. San and M.B. Schadly, Microbiological Associates Inc., Laboratory Study No. T8728.501014, 12/28/89). DEET (purity = 98.3%) was used at concentrations of 0 (DMSO), 28, 83, 278, 833, 2778, or 8333 ug/plate (no S9) and at 0 (DMSO), 2.8, 8.3, 28, 83, 278, or 833 ug/plate (+ S9, derived from Aroclor 1254 induced rat liver) were assayed with Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537 and TA1538. The response for mutagenicity was not positive in the presence or absence of Aroclor 1254 induced rat liver metabolic activation system. ACCEPTABLE. (Kishiyama & Silva, 6/5/91).

023 003284, "Mutagenicity Plate Assay", (Litton Bionetics Kensington, MD, LBI Project No. 20838, 1/80). Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, TA-100, Saccharomyces cerevisiae D4 also tested; No dose concentrations stated. No adverse effect indicated, but insufficient information presented for independent adverse effects assessment; Summary UNACCEPTABLE. (J. Remsen 4/18/85).

004 926118, "Mutagenicity Evaluation of M-Deet, Stock No. 6840-8645428, Final Report" (Litton Bionetics, Kensington, MD, LBI Project No. 2547, 7/15/76). S. typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, TA-100 and S. cerevisiae strain D4; Deet (no purity information); 0, 0.01, 0.1, 1.0, 5.0 ul/plate; 1 plate per concentration, single trial + rat liver activation. No adverse effect indicated; Incomplete (insufficient protocol information, no QA report), UNACCEPTABLE, not upgradeable (no repeat assay, insufficient number of replicates). J. R. Gee, 9/25/87.

CHROMOSOMAL ABERRATION

** 084 090999, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells", (D. L. Putman and M. J. Morris, Microbiological Associates Inc., Laboratory Study No. T8728.337, 12/28/89). DEET (purity = 98.3%) was used at concentrations of 0 (DMSO), 0.063, 0.125, 0.250, or 0.50 ul/ml with Aroclor 1254 induced rat liver S9 (10 hour harvest) or at 0 (DMSO), 0.125, 0.250, 0.50, or 1.0 ul/ml without metabolic activation (18 hour harvest) with Chinese Hamster (CHO-K_7) Cells. Treatment exposure time was 16 hours (no S9) or 2 hours (with S9). 500 cells/culture were assessed for mitotic index (duplicate cultures). The percentage of cells with structural aberrations did not increase significantly with DEET treatments relative to the control. ACCEPTABLE. (Kishiyama & Silva, 6/10/91).

028 035483, "Investigation of N,N-diethyl-M-toluamide (M-DET for Dominant Lethal Effects in the Mouse" (U.S. Army - Environmental Hygiene Agency, Study No. 51-034-78, 11/77). DEET (95% meta isomer, remainder ortho & para) administered to male mice by oral gavage at 600 mg/kg, 10 male mice/group; Slight adverse effect on the outcome of pregnancy in untreated females but no conclusive dominant lethal effect; the single dose showed no toxic effects on males, Incomplete (missing some individual data), UNACCEPTABLE - Not upgradeable (only one dose level, too few

pregnant females per group). (J. Remsen 10/4/85).

DNA DAMAGE

** 084 090998, "Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with a Confirmatory Assay", (R. D. Curren, Microbiological Associates Inc., Laboratory Study No. T8728.380009, 12/22/89). Deet, purity 98.3%, at concentrations of 0 (DMSO), 0.003, 0.01, 0.03, 0.1, 0.2, or 0.3 ul/ml were assayed with primary rat hepatocytes. Exposure time was 18-20 hours. Relative toxicity averaged 65% for the high dose (0.3 ul/ml) in the initial assay, 35% and 21% for the 2 highest doses (0.3 and 0.2 ul/ml) in the repeat assay. An increase in net nuclear grain counts was not observed in either assay. ACCEPTABLE. (Kishiyama & Silva, 6/10/91).

NEUROTOXICITY

118 112057 "Neurotoxicity Evaluation in Rats Following Multigeneration Exposure to DEET," (Schardein, J.L., International Research and Development Corporation, January 23, 1990; project 555-015). Charles River CD rats (20/sex/dose) obtained from a 2 generation rat reproduction study with DEET were used in this study (090996, IRDC study 555-009). DEET (N,N-diethyl-m-toluamide; 98.301% pure) was administered in diet to the F2 offspring at 0, 0 (sham control), 500, 2000 and 5000 ppm (same concentrations as had been used in the original study) for 9 months. The "sham control group" was for the passive avoidance testing. At the time of neurotoxicity evaluation, these F2 offspring were approximately 40 weeks of age. Neurotoxicity evaluations were conducted over an 8 week period. NOEL = 500 ppm (Significant decreases in body weight was observed in both sexes at $\geq$ 2000 ppm. Motor activity effects were also noted at 5000 ppm in both sexes.) **No adverse neurological effects were observed.** These data are supplemental. M. Silva, 1/16/92.

119 112079 "Neurotoxicity Evaluation in Rats Following Acute Oral Exposure to DEET," (Schardein, J.L., IRDC, 1/23/90). DEET technical (98.301% pure) was administered to Charles River Crl:CD VAF/Plus rats (10/sex/dose) by gavage at 0 (white mineral oil), 50, 200 and 500 mg/kg in one dose. Evaluations for neurotoxic effect were performed at 1 hour, 24 hours and 14 days following DEET administration. NOEL = 200 mg/kg (Decreased food consumption--females, increased vocalization--males, increased thermal response time--both sexes and decreased motor activity--both sexes at 500 mg/kg). These data are supplemental. M. Silva, 1/15/92.

METABOLISM

006 926121 "Comparative Study of the Resorptive and Excretory Properties of Certain Repellents," (Gleiberman, S.E., Voronkina, T.M., Latyshev, V.I. and Tsetlin, V.M., All-Union Scientific-Research Institute of Disinfection and Sterilization, USSR Ministry of Health, Moscow. Published in Med. Parazitol. Parazit. Bolezni, 43:446-455, 1974). DETA (and 7 other chemical repellents from the class of mono- and di- substituted amides of organic acids: valeric, benzoic, M-toluic, phenoxyacetic), in a 40% solution (in 70% alcohol) was administered to the backs of shaved (180-200 sq. cm) rabbits (1.2 ml/kg; 7 mg/1 sq. cm in active substance). Absorption was assayed at 30 min., 1, 2, 3, 4, 5, 6, 7, 8, 24, 48, 72 and 96 hours after application by removing

blood samples and analyzing urine (approximately 5 rabbits/test chemical were used--It's not really clear, since 42 rabbits were used for 8 chemicals). The repellents were coarried on the skin for 8 hrs before being washed off with water (pg. 6). Results showed DETA attained maximum concentration in blood at 2 hours and began to disappear at 48-72 hrs. A correlation was found between the ratio of the solubility in olive oil and solubility in water and the concentration of DETA in blood after 8 hrs. DETA has an affinity for organs rich in lipids (brain, adrenals, fat) and (hair on the application site). The maximum concentration in urine was primarily in the first 8 hrs after application. These data are supplementary. M. Silva, 7/8/91.

028 035484 "Behavioral Effects of Acute Aerosol Exposure to N,N-Diethyl-meta-toluamide (M-DET), Joyce, B.E., Department of the Army, US Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD, 1979. M-DET (95% meta isomer; LOT #: 7141) was used in an inhalation study on Sprague-Dawley rats at 0 (air), 2300, 2900, 4100 mg/m3 (10/sex/dose) for a 4 hr whole body exposure (breathing zones were measured at 1/2, 2 and 3 hours). Behavioral tests were performed as soon as the exposure period ended (activity, endurance, balance). There were no toxic signs at necropsy but behavioral tests showed that a combination of behavioral tests could be used to differentiate between treatment levels of M-DET and that behavioral measures can differentiate between groups of animals receiving concentrations below those causing any gross physical changes or toxic signs and controls. These data are supplemental. M. Silva, 7/9/91.

028 035485 "Behavioral Effects of Subchronic Aerosol Exposure to N,N-Diethyl-meta-toluamide (M-DET)," (Brendan, E.J., Department of the Army, US Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD, 1979). M-DET (no purity stated, but assumed to be the same as used in study 035484 = 95% meta isomer; LOT #: 7141) was used in a subchronic inhalation test for 6 hrs/day, 5 days/week on rats (assumed to be Sprague Dawley as in 035484--10/sex/group) for 13 weeks at 0 (air), 250, 750 and 1500 (1/4 LD50) mg/m3. Tests for toxic signs as well as behavior (balance, tactile sensitivity and endurance tests during weeks 2, 4, 6, 8, 11 and 13) were performed. Behavioral effects were observed at each level that made the doses distinguishable from eachother and the control. No toxic effects were observed at any dose. According to the report, a person may be exposed to 0.7 g/m3 M-DET in a 10 second spraying (56 g aerosol can; 71% m-DET; at 1 g/sec in a 10 m3 room). At 250 mg/m3, the exposure is 2.8 times lower, but the exposure was for hours rather than seconds. However, if M-DET produces the major effects through skin penetration, rather than inhalation, the expected use levels could be similar to the medium concentration depending on how much is actually applied and how often applications are repeated. The report stated that there were significant changes observed in this study but not in a clear dose-response fashion. It was recommended that no change in use of M-DET products be made, however further tests should be performed. M. Silva, 7/9/91.

028 035491 "Dermal Penetration of the Radiolabelled Repellent, N,N-Diethyl-m-Toluamide (M-DET)," (Mazur, J.F., Department of the Army, US Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD, 1980). Radiolabelled m-DET (ring 14C; 13.6 mCi/mmol; 98% radiochemical purity) was used in several studies: A. **Single I.V. Administration**: [14C]-m-DET was administered by i.v. to New Zealand White rabbits (6 females), Sprague-Dawley rats (3/sex), and dogs (3 males) at 2, 5 or 10 uCi/animal for rats, rabbits and dogs, respectively. Blood was drawn from dogs prior to injection and at (unspecified) "timed intervals." Urine was collected daily for 7 days. Results showed renal excretion was the primary route, usually within the first 24 hours (rats = 87%-90% no sex difference, rabbits = 74%; dogs = 46%). Elimination by feces was < 3%/species and low (≤ 1.8%) radioactivity was detected in organs (liver, lung, spleen, kidney, and

skin (also bone and muscle in female rat only). B. **Single Topical Application**: m-DET was applied to each species in the clipped midlumbar region of the animal's back (4 ug/cm2, same dose level as the radioactive i.v. counterparts--2, 5 or 10 uCi). After application, the area was covered with petrolatum while the solvent dissolved, then it was covered with a nonocculsive patch. The patch was changed at 24 hours and the new one stayed on for the next 7 days. Urine and feces were collected and monitored for the 7 day period. Results showed 43, 32, 36, and 31% recovery of radioactivity in urine, 28, 31, 22, and 32% in the 24-hour patch for male and female rat, rabbit and dog, respectively within the first 24 hours. Radioactivity in feces was ≤ 2%, 7-day patch at ≤ 7% and skin application area was ≤ 15% for all. Excretion was essentially complete by 3-4 days, although absorption continued throughout the 7 days. Radioactivity recovered in tissues (liver, lung, kidney, muscle and skin from female rat--none from males; liver and lung from rabbits; liver, lung, spleen, kidney and testes from dogs) showed only trace amounts. C. **Repeated Topical Application:** M-DET (75% w/v in ethanol + 0.5 uCi/day of radioactivity) was applied repeatedly to pregnant rabbits at 50, 100 or 500 mg/kg/day from day 1-29 of gestation (4/dose). Nonocclusive patches were monitored for volatilized radioactivity at days 14 & 29. Urine was collected daily and tissue samples were collected on day 29. Fetuses were surgically removed and assessed for radioactivity content. Results showed a steady state for absorption/elimination at approximately 45% of each day's dose, which began in the first 24 hours and continued throughout the study (unaffected by different dose levels). There were trace amounts in the liver, lung, spleen and fetuses. At term, the 500 mg/kg/day group showed 20, 8, 30, and 8 ppm in liver, spleen, kidney and skin, respectively (1 rabbit), 10 and 20 ppm in kidney and bone (1 rabbit) and nothing (2 rabbits). Analysis of blood at term showed there was no detectable radioactivity. D. **Single I.V. Injection to Pregnant Rabbits:** 12 Pregnant rabbits (day 15 of gestation) were administered a single i.v. dose of 15 uCi radioactivity, then at intervals of 1, 3, 6 and 24 hours after dosing, animals were terminated. Blood and tissue specimens were taken from all animals. Rabbits surviving 24 hours, were sampled beginning immediately after injection and at timed intervals thereafter. Results showed blood levels reached a peak at 15 min. At 24 hours, trace amounts remained in liver, lung, spleen, kidney, brain, blood and fetuses (fetuses showed the lowest radioactivity of all specimens). E. **Quantitation:** Urinary and fecal excretion of [14C]- M-DET radioactivity, following a single i.v. or percutaneous (p.c.) dose was quantitated over a 7-day study. Samples were taken from brain, lungs, liver, kidneys, spleen, testes, skin, muscle (thigh), fat (omental), bone (femur) and skin from the application site. Results showed no difference in distribution and elimination between to two routes. The compound probably penetrates the skin with little metabolism, then is metabolized by the liver and is eliminated in the urine.
DISCUSSION: An insect repellant should have maximum repellency without appreciable absorbancy. m-DET appears to be highly absorbed. It has been shown (by literature studies cited in the report) that less than 9% absolute absorption of labelled m-DET occurred in humans after a 24 hour dermal exposure and a 5 day collection period. Another study showed 5.5 and 3.8% absorption of topical m-DET in 2 separate 8 hour exposures and 48 hour collection periods. Animal studies, however show a very high level of absorption (a depot effects where m-DET was maintained in the skin with a subsequent slow release into the blood. Human studies showed evaporative loss to be approximately 48%, where animal data in this study show much lower percentages, perhaps due to greater absorption. Dogs showed the lowest absorption of all species and was most like humans. According to the report human and dog absorption/elimination kinetics were highly correlated (although dog absorbed 31% and humans absorbed 9%) for example, if the values for the first 3 days measure 76 vs 78%, 13 vs 12% and 4 vs 5% for dog and human. The differences in absorption can be explained by the difference in skin structure. It was reported in the literature that appendageal diffusion of topically treated human skin in vitro occurred in the first

2-3 hours, followed by a steady-state diffusion from the stratum corneum. Animal epidermis, containing greater numbers of hair follicles/cm2, as well as more complex duct networks, would tend to have facilitated diffusion. Beyond that, the limiting factor is the thickness of the stratum corneum as the steady-state absorption predominates. Apparently polar alcohols diffuse through follicles easily and absolute alcohol was used in animal studies (and some commercial preparations). Although the alcohol was allowed to evaporate (15 min), maximal absorption in the first hour was facilitated. It was recommended that the solvent used be considered in human-use formulations.

Regarding fetal exposure, it appears that m-DET is not metabolized by the rabbit fetuses at the stage of maturation measured (day 15 of gestation). Human fetuses, however, beyond the first trimester have drug-metabolizing enzymes whose rate of metabolism are 30-50% those of human adults. Human fetal kidney is also capable of excreting metabolites. Although there is no bioaccumulation of m-DET radioactivity in rabbit fetuses, it does not mean the same thing occurs in human fetuses.

024 019115 "Distribution and Fate of the Insect Repellent 14C-N, N-diethyl-m-toluamide in the Animal Body. II. Distribution and Excretion after Cutaneous Application," (Blomquist, L. and Thorsell, W., The Department of Pharmacology, Royal Veterinary College, Uppsala and Department 5, National Defence Research Institute, Stockholm, Sweden. Published in Acta Pharmacol. et Toxicol., 41:235-243, 1977.) This study shows [14C]-DEET (98% pure, 6.0 mCi/mM) distribution in male NMRI mice after dermal administration (0.3% in 20% ethanol) on depilated skin and the amounts of radioactivity excreted into the urine after cutaneous application of [14C]-DEET (25% solution in absolute ethanol--highest concentration used in most commercial preparations) in one human adult female volunteer. Whole body autoradiography was performed on 3 mice treated on 3 x 3 cm depilated skin with 10 uCi of [14C]-DEET and sacrificed at 2 hours (at which time the treated skin was washed with ethanol), 6 and 36 days. Two mice were treated as described above but the smeared skin of each mouse was cut out and assayed for autoradiography. Six mice were treated with [14C]-DEET, as described above, and urine was collected at 2 hours (treated skin washed with ethanol). The animals were then placed in metabolism cages and urine was collected for 2 days. The human subject was treated with 0.03 ml on a forearm (3 x 3 cm area), corresponding to 0.12 mg/kg body weight. After 8 hours, the area was washed with ethanol. Urine was collected for 2 days. **Results** of the mouse whole body autoradiography showed the highest concentration of radioactivity in the lacrimal gland, liver, bile, intestinal contents, kidney, urine and nasal mucosa. Urinary excretion in mice was highest 6 hours after treatment whereas the human subject showed maximal excretion after 12-18 hours. Mice showed a low, but significant excretion which persisted throughout the one month observation time. M. Silva, 7/1/91.

024 019116 "Distribution and Fate of the Insect Repellent 14C-N,N-diethyl-m-toluamide in the Animal Body. I. Distribution and Excretion After Injection into Mice," (Blomquist, L., Struman, L. and Thorsell, W., Department of Pharmacology, Royal Veterinary College, Stockholm and Department 5, Research Institute of the Swedish National Defence Sundbyberg 4, Sweden, 1974. Published in Acta Pharmacol. et Toxicol., 37:121-133, 1975).
N,N-Diethyl-m-toluamide-carbonyl-14C was administered i.v. to mice as follows: **Group I** consisted of male NMRI mice treated at 0.5 uCi (0.5 ml of a 0.03% solution)/10 g body weight. Then at 1, 5, 20 and 60 minutes; 4 and 24 hours, animals were sacrificed (5/group). Samples of blood, liver, kidney, brain, skeletal muscle and exorbital lacrimal gland were removed, weighed and counted by LSC. **Group II** had the same treatment as group I, except 7 (half) of the animals had free access to food and the remaining 7 were starved for 18-24 hours before the experiment. Access to water

was unlimited and survival time was 5 min. In **Group III**, whole body autoradiogaraphy was performed on 5 males and 2 females (advanced pregnant) treated i.v. with 5 uCi of [^{14}C]-DEET/10 g body weight. This group was sacrificed (1/time point) at 5 min., 20 min. (female), 1 hour, 4 hours (female) and 1, 4 and 16 days. Sagittal sections, throughout the body were examined. **Group IV** was an excretion study: A. **Urine**: 4 mice were injected i.v. with 1 uCi [^{14}C]-DEET and put in metabolism cages. At 8, 24 and 48 hours, urine was collected. B. **Feces**: 4 mice were treated as in "A", but feces were collected. C. **Expired CO_2**: 2 mice were given 1 uCi of [^{14}C]-DEET i.v. and placed in a 500 ml polyethelene vial. The same time points were used for collecting CO_2 samples as in "A" and "B". **Results** showed after i.v. injections, highest tissue concentrations of radioactivity were found in liver, kidney, lacrimal gland and nasal mucosa. At short intervals after treatment, concentrations above the blood level were recorded in thyroid and brown fat. Quantitatively, the highest uptake and retention was in the lacrimal gland. The compound was excreted rapidly through the kidneys, and by 4 hours post injection little remained in all tissues, except lacrimal gland. There was a placental barrier for the compound (much lower concentration in the fetuses than in the mother). M. Silva, 7/1/91.

024 019122 "Fate of C14-Diethyltoluamide Applied to Guinea Pigs," (Schmidt, C.H., Achee, F. Jr. and Bowman, M.C., Entomology Research Division, Agric. Res. Serv., USDA, published in the Journal of Economic Entomology, Vol. 52(5):928-930, 1959.) The evaporation and absorption of C14-diethyltoluamide (12.13 uci/gm) on skin of guinea pigs (1/group) was studied. After adding the compound at 6.97, 7.11 (labelled compound) or 7.14, 6.21 and 6.63 (unlabelled compound) to shaved dorsal skin, the animals were placed unrestrained in a metabolism cage (with constant air flow to facilitate evaporation). Urine and feces samples were collected throughout the study. After 6 hours, the animals were removed and the treated surface was rinsed with 500 ml of ethanol. Blood samples were taken from the foreleg and skin biopsies were taken from the treated area at intervals. Results showed the amount of compound absorbed was 1.32, 3.40, 3.04, 1.21 and 2.62 mg/sq in. but the amount evaporated was consistent (0.96, 0.98, 0.89, 1.02 and 0.90, respectively). The residual was recovered in the rinses. Radioactivity in blood, skin and hair was assessed up to 198 hours post treatment in the two pigs treated with radiolabel. Peak radioactivity in urine was reached within 12 hours of application and > 80% was excreted in urine within 24 hours and 89% within 48 hours. There was no unchanged diethyltoluamide in the urine. A total absorbed dose of 92.78 and 94.61% had been excreted in urine after 168 hours (0.74 & 0.75% in feces; 1.38 & 0.03% remained in skin and 0.0 & 0.56% in hair), with 95% recovery (overall recoveries of applied dose was 99 & 98.1%). These data are supplementary. M. Silva, 6/26/91.

042 054552-53**,** 055360, 055362, 055814-15, "Pharmacologic and Toxicologic Studies on N,N-Diethyltoluamide I. N,N,-Diethyl-m-toluamide," (Ambrose, A., Toxicology Division, United States Army Environmental Health Laboratory, Army Chemical Center, MD. Published in Toxicology and Applied Pharmacology, 1(1):97-155, 1959. M-DET (85-95% pure) was used in several studies:

I. INTRAGASTRIC ADMINISTRATION:

LD50 determinations were made using albino rats (5-15/sex/dose) and 3 different samples of m-DET (using either polypropylene glycol or cottonseed oil as a vehicle) at several unspecified doses. A stable emulsion was prepared by combining 40 ml m-DET with 0.5 g vegetable lecithin, 5 ml ethanol and 55 ml distilled water and administered by gavage. Animals were observed for 7 days following treatment. Results were similar, regardless of sex, grade of m-DET or carrier vehicle (Males = 1.8 - 2.7 mg/kg, Females = 1.75 - 1.8 mg/kg, Sexes combined = 2.25 - 1.97

mg/kg, Samples combined = 2.0 mg/kg). Animals administered lethal doses showed hyperemia at the base of ears, lacrimation, chromodacryorrhea, depression, prostration, epileptoid tremors and asphyxial convulsions. Respiratory usually preceded cardiac failure. At doses near but below the LD50 rats showed milder symptoms and in some cases, rats that appeared moribund, completely recovered within 24 hours. Rats that survived for more than several hours recovered with no apparent toxic effects. Gross postmortem showed that in cottonseed oil, m-DET produced some hyperemia.

II. I.V. ADMINISTRATION:

Acute and subacute effects in albino rabbits was studied, using the emulsions described above. **Acute** toxicity used single i.v. injections of 25, 50, 75 and 100 mg/kg m-DET (3 rabbits/dose). At $\geq$ 75 mg/kg all animals died within 1 min. No deaths occurred at the other doses. Temporary miosis (3 min. in duration) and respiratory stimulation were reported in rabbits at 50 mg/kg. Observations were continued over 30 days post injection. The **subacute** toxicity study used 5 repeated daily doses of 25 mg/kg. No effects were observed. Rapid injections were accompanied by temporary miosis and collapse, however when slowly injected, m-DET induced no effects. The animals were observed for 7 days, then were terminated and necropsied (no effects).

III. PERCUTANEOUS AND CUTANEOUS TOXICITY

Single cutaneous application: Two groups (treated with 2 or 4 mg/kg) of 6 albino rabbits/group were treated with m-DET (half the rabbits/group had their skin slightly abraded). After m-DET was applied to the depilated area of the trunk, each rabbit was covered with an elastic cotton bandage and the animals were immobilized for 24 hours. No mortality occurred. Mild to moderate erythema was reported in all rabbits (slightly more in abraded skin). 24 Hours after removal of the bandage, erythema in animals with intact skin had subsided. Lightly abraded skin erythema disappeared by 5 days. No difference in erythema could be distinguished between the 2 and 4 mg/kg groups.

Repeated cutaneous application: Two groups (5/sex/group) of albino rabbits were exposed to daily (excluding weekends) applications of m-DET 2 ml/kg of 50% m-DET in cottonseed oil or 2 ml/kg of 50% solution in isopropanol)--actual daily amount of m-DET was 1 ml/kg) for 13 weeks (65 applications). Prior to exposure and once/week thereafter the trunk of each rabbit was clipped free of hair. The area of treatment was not covered to prevent oral ingestion by licking the applied material, since m-DET produces some paresthesia on the lips and tongue and has a bitter taste. No mortality was reported. One third of animals (both carriers) showed cutaneous irritation (slight to moderate erythema, desquamation and dryness). Over the weekends the erythema disappeared but the dryness and desquamation persisted. By 3-4 weeks, skin turned leathery, hard and dry with fissures. Lowering the dose to 0.25 and 0.5 mg/kg for 20 days produced the same effect (somewhat less). 3 weeks after cessation of treatment, desquamation, coriaceousness and fissures disappeared and the rabbits appeared normal (some scarring occurred). In addition to the study in rabbits, 5 human volunteers were administered a 50% solution of m-DEET in isopropanol on face and arms once/day for 5 consecutive days (1 ml on face and 2 ml/arm). No irritation occurred but a slight tingling sensation and feeling of dryness occurred. After the 3rd application, desquamation around the nose was apparent in all subjects. This disappeared after 2 days. On one person, applications of undiluted m-DET was administered on the face, daily until desquamation around the nose appeared (by day 3), then resumed after desquamation disappeared (2 days). This continued for 6 weeks, with desquamation, tingling, dryness of the face occurring.

IV. SUBACUTE ORAL INGESTION:

Weanling albino rats (10/sex/group) were treated at 0, 0.01, 0.05, 0.1, 0.5 and 1% m-DET (equivalent to 0 (commercially available ground meal), 100, 500, 1000, 5000 and 10000 ppm) for

200 days before they were autopsied. 3 rats/sex died, but was not dose related. There was a significant decrease in growth at 1% m-DET. Testes:body weight ratios showed an increase at ≥ 0.1% m-DET. The liver:body weight ratios of male rats at ≥ 0.5% m-DET were greater than controls. The kidney:body weight ratios in both sexes at 1% m-DET were increased significantly. There were no histopathological effects.

V. PHARMACOLOGICAL STUDIES:

The effects of m-DET on isolated organs (rat uterus and rabbit ileum) treated with a 40% solution in vitro. Concentrations of 1:10000 m-DET produced no effect on rat uterus, 1:5000 showed depression of the amplitude of rhythmic contraction and tone of varying intensities, 1:2500 showed contraction and tone completely abolished. After rinsing the tissue, contraction and tone were restored to normal. Effects on rabbit ileum were essentially the same as those observed on the uterus, except it was more sensitive (at 1:10000, all intestinal segments responded by decreasing amplitude of rhythmic responses). The effect was reversible. (M. Silva, 7/2/91).

50191-237 167533 "A Blood Level Study in Humans Following Topical Applications of *N,N*-Diethyl-*m*-Toluamide (DEET)" (Ohayon, A., L. Ehler, and K. Denver, L.A.B. Pharmacological Research International, Inc., Quebec, Canada, Laboratory ID EP135, 12/24/97). Plasma levels of DEET were monitored in human volunteers (3 males and 3 females) after dermal application of DEET (97.5% meta isomer) for 4 consecutive days. Females and males were administered at 3 g/day (females) and 4 g/day (males) to one arm and both legs. Blood samples were collected prior to application and at 0.5, 1, 1.5, 2, 3 4, 6, 8 (immediately before showering), 8.5, 9, 10, 12, 14, 16, 20 and 24 hours after application on day 1 and 4 of dosing. There was no evidence of adverse reactions in the subjects that was attributed to DEET. In females, the mean peak plasma concentration decreased from 430 µg/ml on day 1 to 254 µg/ml on day 4. The mean peak plasma concentration in males also decreased from day 1 (618 µg/ml) to day 4 (487 µg/ml). The mean half-life was 6.4 and 5.9 hours in male and females on day 1, respectively. On day 4, the mean half-life was slightly increased in both sexes at 6.7 and 9.0 hours for males and females, respectively. The mean AUC in males decreased from 5.11 µg•hr/ml on day 1 to 3.76 µg•hr/ml on day 4. A similar decrease in the mean AUC was seen in females from day 1 (3.07 µg•hr/ml) to day 4 (2.10 µg•hr/ml). Supplemental. (C. Lewis, 4/12/99).

50191-238 167534 "Blood Level Study in Dogs Following Single Oral Administration, via Gelatin Capsules, of N,N-Diethyl-m-Toluamide (DEET)" (V. Badalone, Bio-Research Laboratories Ltd, Project No. 87607, 10/31/97). Plasma levels of DEET were examined in 4 beagle dogs/sex after administration of DEET (97.48% meta isomer) in gelatin capsules at 75 mg/kg/day for 4 consecutive daily doses. Blood samples were collected prior to dosing and at 10, 20, 30, 45, 60 and 90 minutes, and 2, 3, 4, 6 and 24 hours after dosing of the first dose and final dose. No clinical signs of toxicity or changes in body weights and food consumption were seen during the study. The mean time to peak plasma concentration was around 30 minutes in both sexes. The mean peak concentration was 18.3 and 14.0 µg/ml in males and females on day 1. The mean peak concentration was lower on day 4 at 14.2 and 12.5 µg/ml for males and females, respectively. The mean half-life in both sexes was approximately 28 minutes on both days 1 and 4. The mean AUC were 15.9 and 13.4 µg•hr/ml in males and females, respectively, on day 1. On day 4, the mean AUC were slightly lower at 11.2 and 10.2 µg•hr/ml for males and females, respectively. Supplemental. (C. Lewis, 4/12/99).

50191-239 167535 "Blood Level Study in Rats Following single and Repeated Dermal Applications of N,N-Diethyl-m-Toluamide (DEET)" (J. Laveglia, MPI Research, Inc., Laboratory Study ID 555-

029, 5/7/97). Plasma levels of DEET were examined in 20 Sprague-Dawley rats/sex after a single or 5 consecutive dermal applications of DEET (> 97% meta isomer) at 1000 mg/kg/day. Four rats/sex were euthanized at 2, 4, 8, 12, and 24 hours following the first or fifth application and plasma levels measured. Animals were monitored for mortalities and clinical signs. No signs of toxicity or mortalities were seen. With a single dermal dose, the mean time to peak plasma levels was 4 and 8 hours in males and females, respectively. With 5 consecutive dermal doses, the mean peak time was 8 hours in both sexes. The mean peak plasma levels in males decreased from 5.58 µg/ml after a single dose to 4.83 µg/ml after 5 consecutive doses. A similar pattern was seen in females with the mean peak plasma levels decreasing from 26.60 µg/ml after a single dose to 17.2 µg/ml after 5 consecutive doses. The mean AUC was calculated to be 89.5 and 368.2 in males and females, respectively, with a single dermal dose. While the mean AUC was slightly higher in males (100.8) after 5 consecutive doses, it was lower in females (134.8 µg@hr/ml). The mean half-life was 6.9 and 2.2 hours in males and females, respectively, with a single dose. The mean half-life was slightly higher in both sexes (8.7 and 2.9 hrs for males and females, respectively) after 5 consecutive doses. Supplemental. (C. Lewis, 4/12/99)

50191-240 167536 “Blood Level Study in Rats Following Single Oral Bolus Administration of N,N-Diethyl-*m*-Toluamide (DEET)” (J. Laveglia, MPI Research, Inc., Laboratory Study ID 555-028, 5/7/97). Plasma levels of DEET were examined in 24 Sprague-Dawley rats/sex administered a single dose of DEET (>97% meta isomer) by oral gavage at 200 mg/kg/day. Three rats/sex was euthanized at 15, 30, 45, 60, 90, 120, 180 or 240 minutes after dosing and plasma levels were measured. There was significantly variability in this study in the plasma levels in both sexes during the first 90 minutes after dosing. After confirming that this was not due to an error in the analysis of DEET, the investigator suggested that the differences may be due to variability in the site within the stomach to which these small volumes (~50 µl) were administered or differences in the stomach contents resulting from possible differences in water consumption prior to dosing. The investigator suggested that the higher values at 15 and 30 minutes after dosing more likely reflect the actual DEET blood profile. The plasma levels appeared to plateau within 45 minutes after dosing in both sexes. The mean DEET concentration during the 4 hour period was 9.58 and 13.61 µg/ml in males and females, respectively. The AUC was not calculated since DEET plasma levels did not return to baseline. Supplemental. (C. Lewis, 4/12/99)

MISCELLANEOUS

003 026417 "N,N-Diethyl-M-Toluamide (DEET) Pesticide Registration Standard, 12/80.