Office of Environmental Health Hazard Assessment

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MEMORANDUM

TO: Joyce Gee, Ph.D., Acting Chief
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FROM: Anna M. Fan, Ph.D., Chief
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mgp for AMF

DATE: October 5, 1999

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT N, N-DIETHYL-M-TOLUAMIDE (DEET)

We have completed our review of the draft risk characterization document (RCD) for the active ingredient *N,N*-diethyl-*m*-toluamide (DEET) prepared by the Department of Pesticide Regulation (DPR). DEET is used as an all-purpose insect repellant applied either directly to the skin, or to clothing, bedding and tents of users. In California, over 160 products are registered which contain DEET as the active ingredient, and in 1995, 104,082 pounds of the active ingredient were sold. The principal users are the general public and outdoor workers such as park and forestry personnel. It is estimated that 38 percent of the general public in the United States (U.S.) uses insect repellents containing DEET.

The draft RCD package submitted to the Office of Environmental Health Hazard Assessment (OEHHA) consisted of the draft RCD (June 28, 1999) prepared by the Medical Toxicology Branch. Additional information obtained independently included a summary of toxicology data for DEET (last revised on June 6, 1999) prepared by the Medical Toxicology Branch and a DEET use survey submitted to DPR by a registrant. OEHHA staff also conducted a brief review of the published literature on DEET.

We obtained the document entitled "Human Exposure Assessment for DEET" (January 20, 1999) from the Worker Health and Safety Branch of DPR, which is apparently a final document. OEHHA had not previously reviewed the exposure assessment for DEET. We

understand that the exposure assessment is prepared separately from the RCD by the Worker Health and Safety Branch. However, it is not possible for us to review RCDs without the exposure assessments, and any related documentation. Therefore, it would be helpful if draft exposure assessments were provided prior to (preferable) or together with the submission of the RCD package. Having to obtain the exposure assessment independently might delay our review of the RCD and submission of our comments to DPR.

The draft RCD is well written. The document includes a summary of the extensive toxicological database for DEET. In the risk identification section, the toxicological data are adequately evaluated for relevance to the hazard DEET might pose to exposed humans. This was a difficult undertaking since DEET rarely produced any consistent toxicity across different exposure time frames and animal species. The draft RCD states that seizures have been reported to occur in individuals following exposure to DEET. Experimental animals exposed to DEET might also exhibit seizures and other neurological effects. Other toxicities reported are not as well defined and vary among species and exposure period. Dermal irritation was also reported. Margins of exposure (MOEs) for DEET were determined to be at least 100 for all subpopulations under acute, subchronic or chronic exposures, except for high-end acute exposures to children under 12, for which the margin of exposure was estimated to be ten.

The U.S. Environmental Protection Agency (U.S. EPA) has recently recommended reregistration of DEET [Reregistration of the Insect Repellent DEET (fact sheet) April 28, 1998]. However, this decision apparently was based on a generalized assessment of the toxicity database for DEET rather than a risk characterization based on toxicity endpoints [Federal Insecticide, Fungicide, and Rodenticide Scientific Advisory Panel Meeting, June 1997]. U.S. EPA no longer allows child safety claims on DEET product labels.

Based on our review of the draft RCD for DEET, we feel that the document needs some revision before finalization. In general, the assumptions and conclusions stated in the draft RCD require additional scientific support and analysis, as well as additional detailed discussion regarding exposure assessment in order to provide an acceptable characterization of the risks posed by the use of DEET in California. Our major technical concerns are listed below:

1) There is an inadequate discussion of exposure estimates in the draft RCD.
2) The contribution of inhalation exposure to the overall risk is not assessed in the draft RCD. It is not clear whether this was the result of a limited database, an oversight, or a scientifically based omission. Inhalation is likely to contribute significantly to the overall exposure to DEET in aerosol products.
3) The potential hazards to children, especially those under 12 years old, are not adequately addressed in the draft RCD.

4) The upper bounds of exposure and the degree of DEET absorption appear to be underestimated.
5) Occupational risks are not estimated, despite the stated purpose of the draft RCD to do so.
6) The inclusion of reference exposure levels (RELs) in the RCD would be appropriate in order to compare health-based exposure levels with measured or estimated levels of exposure.

Assuming that the document was revised to address these concerns, the MOEs would be less, indicating an increased hazard potential. We are concerned about the potential for excessive exposures, particularly for products containing high levels of the active ingredient DEET. We are also concerned that the hazards from using 100 percent DEET containing products were not evaluated for the general population and particularly for children under 12.

Thank you for the opportunity to comment on the draft RCD for DEET. If you have any questions about our comments, please contact Dr. Michael J. DiBartolomeis or me at (510) 622-3170.

cc: Joan E. Denton, Ph.D., Director, OEHHA
Val Siebal, Chief Deputy Director, OEHHA
George V. Alexeeff, Ph.D., DABT, Deputy Director for Scientific Affairs, OEHHA
Michael J. DiBartolomeis, Ph.D., PETS/OEHHA
Chuck Andrews, Chief, WH&S/DPR

Attachment

Comments on the Draft Risk Characterization Document
for *N,N*-diethyl-*m*-toluamide

General Comments

The draft risk characterization document (RCD) for *N,N*-diethyl-*m*-toluamide (DEET) is well written. The document includes a summary of the rather extensive toxicological database for DEET. In the risk identification section, the toxicological data are adequately evaluated for relevance to the hazard DEET might pose to exposed humans. This was a difficult undertaking since DEET rarely produced any consistent toxicity across different exposure time frames and animal species. Based on the data, it can be concluded that DEET is as hazardous from acute exposure as from subchronic or chronic exposures based on the actual and derived no-observed-adverse-effect levels (NOAELs).

The exposure assessment portion of the draft RCD is too brief to allow a comprehensive review. Our evaluation included review of the document entitled "Human Exposure Assessment for DEET" (Sanborn, 1999), which was not provided with the draft RCD package. Even with this document prepared by the Worker Health and Safety Branch, it was difficult to follow the exposure assumptions and check calculations. We recommend providing more detail in the RCD on the exposure assessment, and that the Sanborn (1999) document be revised. (More comments follow on the separate exposure assessment document.)

DEET is a relatively low-toxicity pesticide and adverse reactions in humans are uncommon. However, DEET is unique among pesticides in being applied repeatedly, often at high concentrations, directly to human skin. It is, therefore, important to acknowledge in the RCD its potential for overuse, and the resulting possibility of toxic effects, particularly to children. This is addressed in the body of the RCD document, but we recommend that a discussion emphasizing this concern also be provided in the summary.

Dermal absorption appears to have been underestimated in the draft RCD. While whole-body (exposed surface) dermal absorption cannot be accurately determined from the available data, we suggest that 17 percent absorption is a more scientifically defensible mean absorption estimate than the value used (8.4 percent). Twice the estimated mean, or 34 percent dermal absorption, is probably a reasonable upper limit estimate for children. Conditions of the cited human study (Selim, 1991b) clearly underestimate potential dermal absorption under field conditions. A detailed explanation for this comment is provided under Specific Comments.

In addition, the range and population distribution of possible doses with repeated dermal applications is inadequately addressed. Despite the low toxicity of DEET, severe systemic toxic effects have resulted from dermal applications as noted in the "Illness Reports." The conditions or reasons for these overdoses should be more extensively discussed. These were generally repeated-dose applications in which DEET was applied several times, possibly over several days, to a significant portion of the body surface of a child. (See: Fradin, 1998; Qiu et al., 1998;

Brown and Hebert, 1997; Garrettson, 1997; Osimitz and Murphy, 1997; Osimitz and Grothaus, 1995; Veltri, 1994; Robbins and Cherniak, 1986.) The risk of an adverse reaction in this likely "worst-case" scenario should have been included in the hazard estimates and margins of exposure (MOE) calculations.

Major concerns posed in the draft RCD include special sensitivity in humans and potential synergistic toxic interactions of DEET with other commonly used chemicals. Special sensitivity in humans was described in the section "Illness Reports" but not discussed in the "Hazard Identification or Risk Appraisal" sections in any detail that could be developed into a specific recommendation for mitigation (e.g., additional warnings on the label). Similarly, the synergistic interactions of DEET were addressed in the "Toxicity" section with a substantial number of studies illustrating that the toxicities of other chemicals (often pesticides) can be potentiated by DEET. However, no mention of this was made again. Both of these effects suggest that DEET can be more hazardous under some conditions of normal use than would be estimated from the standard toxicity studies. We recommend that the impact of these conditions be factored into the human health risk assessment. If this is not possible based on the available scientific data, then some discussion of this limitation is needed in the technical summary and risk appraisal sections.

Many products containing DEET are sprays, applied by the individual to their clothing or skin. Therefore, it is not clear why inhalation exposure is not addressed in the draft RCD. There is likely to be an inhalation exposure component. If the exposure cannot be estimated, it should be addressed as a limitation and uncertainty in the technical summary and risk appraisal sections.

The inclusion of reference exposure levels (RELs) would be appropriate in order to compare health-based exposure levels with measured or estimated levels of exposure.

Specific Comments

The comments that follow are grouped according to the headings used in the draft RCD. Please note that although a comment may appear under a specific heading, its impact may not be limited to that specific section; it may have relevance to other sections of the draft RCD.

Summary

Page iii states that there is "no evidence of increased sensitivity in infants and children to DEET from available developmental and reproductive toxicity studies." This may be true for studies conducted in experimental animals. However, there is evidence of several cases of young children with acute toxicity resulting from a few topical applications of DEET-containing products as mentioned in the "Illness Reports" section. This may indicate increased children's sensitivity to DEET. Child cases of convulsions and death upon exposure to DEET mentioned in the Illness Reports section should be addressed and recognized in the Summary.

On page iv, it is written that "a review by the Hazard Evaluation Section of OEHHA is acknowledged." This is an obsolete name; it should be changed to "Pesticide and Environmental Toxicology Section." The relevance of the reference to the Adverse Effects Advisory Panel is also unclear.

I. Introduction

Page 2, I. D. Usage. It is stated "It was estimated that approximately 30% of the population used DEET-containing repellents in the last year." Please specify the year referred to.

Page 2, I. E. Illness Reports. This section identifies cases of human intoxication with DEET-containing products. Notably, cases of toxic encephalopathy and seizures and some deaths were reported. A significant number of the intoxications were of children under the age of 12. Although copious or excessive applications of DEET were attributed to be the cause of some intoxications, in one case, a five-year-old boy suffered a seizure after only two applications of DEET (95 percent concentration) in one day. In another case, a 61-year-old woman suffered a severe, short-duration illness after a single application of DEET. In neither case can the reaction be conclusively attributed to the DEET application, although no other potential precipitating events were identified. We recommend that more discussion on the exposure conditions that may lead to such adverse effects be included in this section and in the "Risk Characterization" section.

II. Toxicology Profile

A. Pharmacokinetics: Dermal Absorption. It is clear from this narrative that DEET is rapidly absorbed through skin, although there is uncertainty about relative amount of absorption in different skin areas and under different conditions.

Page 9, first paragraph. The human study of Selim (1991b) is noted as providing the human dermal absorption estimate of 8.4 percent, but no detailed evaluation of the study is provided. The data are also given in Selim et al. (1995), which is the source of details for these comments. For this study, ^{14}C-DEET was applied to the forearms of adult males from a 100 percent product or a 15 percent solution in ethanol. The application site was covered with a non-occlusive dome, and after eight hours the area was washed with isopropanol. Later the epidermis was sampled repeatedly by tape-stripping to assess surface skin reservoir of DEET. Urine and feces were assayed for ^{14}C. Most of the radioactivity was recovered in the isopropanol washes (a mean of 62 percent for undiluted DEET and 52 percent for the 15 percent DEET). Another 21 percent and 25 percent, respectively, was recovered from the dome, and 5 percent and 2.5 percent, respectively, from the application devices. No correction was applied for incomplete elimination of absorbed dose, although recovery losses (6 percent for undiluted DEET and 11 percent for 15 percent DEET) are greater than the estimated urine plus fecal elimination of 5.6 percent and 8.4 percent for the respective preparations. The earlier study of Feldman and Maibach (1970) demonstrated a 52 percent elimination recovery after dermal administration of DEET, compared to recovery after intravenous administration.

We believe that the 8.4 percent value from the Selim study (1995) significantly underestimates the potential for dermal absorption of DEET for the following reasons:

1) The isopropanol wash at eight hours may have more efficiently removed DEET than a standard soap and water wash; in addition, some application periods for outdoor uses may last much longer than eight hours. Therefore, the initial absorption period in normal use can be significantly prolonged compared to the test conditions, resulting in enhanced absorption.

2) Skin sites vary in permeability. In a monkey study, dermal penetration of DEET on the forearm was least among the four sites studied (14 percent on forearm, 33 percent on forehead, 68 percent on the ventral forepaw, and 27 percent on the dorsal forepaw). Variations among human sites have been shown to be similar.

3) Skin permeability is generally greater under hot, humid conditions (where mosquitoes are likely to be contacted), whereas the study was conducted in a medical clinic under controlled environmental conditions.

4) Lack of a correction for percentage of dose collected in urine likely underestimates the absorption by half. This corresponds to the corrected absorption value of 16.7 percent for DEET calculated by Feldman and Maibach (1970) (applied to the forearm, under laboratory conditions).

Considering all of the factors involved, we believe that the Feldman and Maibach (1970) value represents a moderate to low absorption estimate. This value appears more defensible than the estimate from the Selim (1995) study, although the former probably underestimates the potential for dermal absorption of DEET by children in a hot, humid environment. We propose the use of a default "mean" dermal absorption value of 17 percent (rounded) and an upper-limit value of twice that amount, or 34 percent. Alternatively, calculations based on the range of absorptions reported by Robbins and Cherniak (1986) (9 percent to 56 percent, with a mean of 17 percent) could be appropriate. Acute, seasonal, and chronic exposures should be calculated for the upper-limit absorption estimates as well as the mean values because exposure conditions are likely to be consistent with repeated uses for any given individual.

No discussion on inhalation absorption was included in the draft RCD. It is not clear whether that is because there is no information, it was an oversight, or the analysis was omitted for scientific reasons. Inhalation of DEET through aerosols is likely to be a significant source of exposure. The limited discussion on the potential for DEET inhalation exposure in Sanborn (1999) provides a good starting point for a discussion of DEET inhalation in the RCD. We recommend that the exposure assessment (Sanborn 1999) and the RCD be revised to include more information, and if appropriate, more analysis of this potential source of exposure.

B. Acute Toxicity

The numerous toxicity studies conducted on DEET reveal relatively high lowest-observed-adverse-effect-levels (LOAELs), about 1,000 mg/kg by the oral route. Toxicities include prostration, ataxia, and tremors. The LOAEL for systemic effects after dermal exposure was

1,800 mg/kg based on lethargy, extended rear limbs, and hematoma. This was comparable to the LOAEL for acute dermal irritation (about 2,000 mg/kg).

Synergistic interactions of DEET with other chemicals are addressed in a separate section (pages 19 to 23) and are a cause for concern. It appears that interactions may occur among some of the active ingredients in DEET products formulated with other chemicals, as well as with separate products used concurrently with DEET. However, the potential toxicological consequences of such interactions are not addressed in the draft RCD. We recommend providing a relevant discussion in this section as well as in the "Risk Characterization" section.

C. Subchronic Toxicity

The notable findings for subchronic experimental exposures to DEET are male rat nephropathy, decreased kidney weight, increased liver weight, and decreased body weight. The rat nephropathy was judged to be associated with α_{2u}-globulin accumulation, and thus not relevant human health, since humans do not produce α_{2u}-globulin.

Decreased kidney weight in dogs was judged to be an adverse effect. The increased liver weights were observed in a number of studies without concurrent evidence of histopathological changes, and were assumed to be "an adaptive response rather than an adverse effect" (page 24, first paragraph). Body weight decrease was observed after multiple routes of administration, and was considered to be an adverse effect. The lowest LOAEL by the oral route was 200 mg/kg-day for dogs and 300 mg/kg-day for rats by the dermal route. For both studies, the no-observed-adverse-effect-level (NOAEL) was 100 mg/kg-day. The LOAEL for dermal irritation was 100 mg/kg day. These results mirror the range of sensitivity to DEET that was exhibited in the chronic studies.

The computation of the high dose level for the Goldenthal subchronic diet dog study (1995) is problematic. In this study, the high dose group of 6,000 ppm rejected ingestion of the DEET diet, which was subsequently reduced several times in an attempt to accommodate this rejection. However, the reduction in concentration did not solve the problem. The result was that the highest dose group exhibited the most toxicity, but the average daily dose over the eight-week study is less than the next highest dose. It is likely that the toxicity exhibited in this high-dose group is the result of the initial ingestion of the high dose rather than the average dose received during the exposure period. Thus, it does not appear appropriate to list a "LOEL" (lowest-observed-effect-level) of 12 mg/kg-day and "NOEL" (no-observed-effect-level) of 92 mg/kg-day for the same study in this section (page 29) and in the "Hazard Identification" section (Table 18, page 55). We recommend that the RCD not include any conclusion about the dose-response of DEET from the results derived from the highest dose group in this study.

D. Chronic Toxicity

The sensitivity for adverse effects from chronic oral or dermal exposures to DEET in experimental animals was similar to that seen with subchronic exposures. No evidence of DEET-related increases in tumor formation was found. An increase in hepatic hyperplastic nodules and bile duct hyperplasia observed in mice treated with 1,000 mg/kg-day was judged to

be treatment- related and to be a potential preneoplastic event. Hyperplastic liver nodules are a rather common pathology in older mice. It would be helpful if a discussion of any evidence that this increased nodule incidence is within the range of incidence in historical control populations was included in the RCD.

It is not clear why rat renal nephropathy for tumor formation is discussed in the "Summary" for this section when it is not addressed in the individual study summary which is found later in this section.

From both chronic rat and dog oral studies a NOAEL of 100 mg/kg can be identified. A transient increase (observed at interim sacrifice periods of 6, 12, and 18 months but not at study termination) in female rat cholesterol levels was noted at the 400 mg/kg dose and attributed to DEET exposure. From the chronic dog study, a LOAEL was identified based on changes to hemoglobin levels, hematocrit, liver, lymph nodes, and uterus at 400 mg/kg.

F and G. Reproductive and Developmental Toxicity

From the several reproductive studies conducted on DEET, the most reproducible effect was an increased incidence of abnormal sperm; the "NOEL" for this effect was judged to be less than 100 mg/kg-day. It is not clear if the increase in sperm abnormalities was in number or in type or both. Slight increases in anomalies and changes in fetal and maternal body weights appeared within the same dose range as the effects noted in other studies.

III. Risk Assessment

A. Hazard Identification

For the acute local (dermal irritation) risk assessment, we agree with the selection of the most appropriate study and endpoint for the LOAEL/NOAEL determination in the draft RCD. However, for the acute systemic risk assessment, we do not agree with the selection of the most appropriate study and endpoint for the LOAEL/NOAEL determination in the draft RCD. We realize that there are several factors used when selecting appropriate toxicity endpoints. However, the criteria used in the draft RCD for selecting the appropriate studies were not clearly delineated. The appropriate studies for determining the NOAEL/LOAELs would be those in which DEET was administered dermally, which is the predominant exposure route. The draft RCD used oral studies for risk determination. However, the rationale or explanation for selecting oral studies is not clear or adequately presented in the draft RCD. Furthermore, it appears that the draft RCD places its emphasis on studies that meet Federal Insecticide, Fungicide, and Rodenticide (FIFRA) requirements, while excluding from risk assessment those that did not.

We recommend that the selection of the critical study for risk determination for acute systemic effects be reconsidered. The draft RCD concludes that the single dose rat gavage study (Schardein, 1989) is more suitable for acute risk determination than the developmental, reproductive, or dermal toxicity studies listed under acute effects (Table 17). The criterion appears to be whether or not a study met FIFRA requirements. For acute systemic effects, an oral rat study was selected in which the "NOEL" was 900 mg/kg (adjusted for pharmacokinetic

considerations from a "NOEL" of 200 mg/kg). Among the dermal studies, the results from one study indicates an increase in preimplantation loss (this is a systemic effect which is interpreted as a potential acute effect apparently following internal DPR policy) at a LOAEL of 100 mg/kg. This rat dermal developmental toxicity study (Gleiberman et al., 1975) was not used because, according to the draft RCD, it did not meet FIFRA requirements. The estimated NOAEL from this study would be 10 mg/kg after applying an uncertainty factor of 10 to the LOAEL of 100 mg/kg-day (without route adjustment factor). Similarly, from another oral developmental study in rats (Sterner, 1977), a NOAEL of 90 mg/kg (adjusted from a NOAEL of 20 mg/kg) could be used. The problem with the selection criterion used in the draft RCD is that it excludes a body of data that indicate the toxic effect occurs at lower doses. The exclusive use of the data from the Schardein (1989) study is not the best scientific or public health approach for this risk assessment. Therefore, we recommend that the revised RCD reassess the body of evidence and reconsider the use of the higher adjusted NOAEL of 900 mg/kg when lower NOAELs have been identified. We also recommend that the selection criteria for the critical studies and toxicological endpoints be clearly delineated in the RCD. If the higher dose oral study is to be used, there should be some scientific explanation in the RCD for not using the lower dose oral or dermal studies.

The oral/dermal dose-route correction that has been used (a factor of 4.5) is specific for rats. The relative areas under the plasma concentration curve after oral and dermal exposures are a function of both absorption and metabolism rates. No evidence has been presented to suggest that the ratio of these two rates is the same in humans as it is in rats. We expect that it would not be. Further examination and discussion of these issues would be needed before this general assumption should be accepted for this risk assessment.

The subchronic studies reveal a wider range of systemic effects, but the comparable LOAELs were not much lower than those observed in the acute studies. Effects were mostly of minor toxicological importance, such as changes in clinical chemistry, slight histopathological changes in the kidney, and signs of increased liver metabolic activity. Body weight reduction was common, which was at least partly attributable to decreased food intake. The critical NOAEL for subchronic exposure (which was used for the seasonal exposure risk assessment) was based on a dermal study by Johnson (1997) with a NOAEL of 300 mg/kg-day, and when adjusted for 40 percent dermal absorption, resulted in an absorbed dose of 120 mg/kg for systemic effects. We agree that dermal studies should be used whenever possible and support using this determination to arrive at a subchronic NOAEL.

The estimated NOAEL of 10 mg/kg for dermal irritation from the subchronic exposure study is the same as from the acute exposure study. Both were estimated from a LOAEL 100 mg/kg, divided by 10 to derive a NOAEL from a LOAEL (see page 57). We agree with this determination.

The NOAEL determination for chronic exposure was similar to that of the subchronic exposure. Unadjusted NOAELs for several studies were about 100 mg/kg-day. Thus, there was little evidence for increased severity upon prolonged dosage with DEET. Although we may agree that DEET may not severely impact major organ systems upon prolonged exposure, we do feel that

there may be limitations inherent in the chronic experimental studies that do not address major neurological effects seen upon human exposure to DEET.

Since there was no evidence of carcinogenicity, and genotoxicity studies were negative except for one dominant lethal assay with equivocal results (page 59, second paragraph), no carcinogenic assessment was conducted. We agree with this determination.

More consistency in presenting information in Tables 17, 18, and 19 would be helpful. It is difficult to compare the dermal doses when one is presented in mg/cm^2 and another on a body weight basis. When computing the MOEs later it is clear that applied oral and dermal doses are converted to absorbed doses (as described in the narrative on page 54). It would be helpful if these summary tables included the adjusted absorbed doses so appropriate comparisons among dermal and oral studies, for acute, subchronic, and chronic studies can be made.

Page 55 and "Reference" section. There is an improper reference to Dourson and Strata; it is Dourson and Stara.

B. Exposure Assessment

The draft RCD refers to the exposure assessment entitled "Human Exposure Assessment for DEET" (Sanborn, 1999), which was not submitted for our review and which we obtained from the Worker Health and Safety Branch with a significant delay. The exposure assessment is a critical part of any RCD, which in the past has been attached to the RCD as an appendix. In general, we recommend that the draft RCD be revised to provide more details on the assessment of exposure in the main document. Attaching the exposure assessment document would also enhance the RCD and make it easier to follow.

We are concerned that the separate exposure assessment document (Sanborn, 1999) was finalized without OEHHA review. We submit the following comments on the draft RCD as well as the separate exposure assessment document with the expectation that the exposure assessment will be revised, as appropriate, based on our comments.

The mean and upper limit values for the daily exposure estimate for DEET is derived from a public survey funded by the registrant (Boomsma and Parthasarathy, 1990). The upper end estimates for acute dermal doses were assumed to be three times the average amount applied during a single application. The estimates of seasonal exposure are based on average exposures, applied only "7.5" times. Although this is a mathematical average, there is no practical means to apply a partial dose of DEET. Therefore, we recommend that reference to frequency of applications be presented in whole numbers (e.g., an average of seven or an average of eight applications). In addition, this seasonal exposure estimate does not include the range of exposures among normal users, and does not address the observed toxicity problem caused by repeated heavy usage of DEET. The user surveys conducted by Boomsma and Parthasarathy (1990) provide information on the distribution of use patterns, which should be included in the exposure assessment and considered in the RCD.

Slow absorption through the dermal pathway may contribute to cumulative toxicity. Based on information on the distribution of cumulative doses over a few days or a use season, particularly for children, an estimate of the potential for adverse effects could be produced. We recommend that the exposure assessment and the draft RCD be revised to include an appropriately detailed discussion of the patterns of use that have resulted in toxic effects.

Pages 59 to 60, Non-occupational exposures. The exposure estimates in Sanborn (1999), derived from the registrant-sponsored studies described in Boomsma and Parthasarathy (1990) appear to contain inconsistencies. Average daily exposures are listed as 0.038 grams/day in Table 11 and 0.65 to 1.07 grams/day in Table 13, with no explanation of the difference. Reference to the original tables of Boomsma and Parthasarathy (1990) did not clarify the problem. However, the higher values (~ 1 gram/day) appear to be representative of moderately high daily dermal exposures, by comparison with the estimated occupational dermal exposure of 4.25 grams/day for workers in the Florida Everglades that was provided in Table 17 of Sanborn (1999). Although it is acceptable to apply these non-occupational dermal exposure values to the draft RCD dose estimates in Table 20, page 60, we recommend that the conditions that result in these exposure estimates be better defined in the documents.

For the calculation of Seasonal Applied Daily Dose (SADD), using only the average seasonal usage of "7.5" applications does not address the issue of potential over-exposures, and the resulting toxicity. We recommend including more information and discussion of the distribution of uses under different conditions.

We agree in general that conditions similar to those in the Everglades would be infrequent in California, as stated on page 18 of the exposure assessment document (Sanborn, 1999). However, some estimate of the range and distribution of exposures to DEET, which are relevant to California, should be derived. Use of three applications in one day (for the acute exposure estimate) as the only measure of high-end exposures is clearly inadequate for the assessment of possible (and likely) applications. High-end dose estimates should be provided for Annual Applied Daily Dose (AADD) as well as for SADD. These dose estimates should consider the variability in absorption (as discussed above), the variability in application rates (amount per application), and the variability in number of applications per season and per year. This will presumably result in some MOEs much less than 100, particularly for children. The relevance of these high-end exposure estimates to the reported toxic effects should be discussed, and the conclusions of the risk characterization for children should be carried over to the "Summary" section.

The first paragraph of the draft RCD Summary (page ii) states that exposures of park and forestry workers are to be considered. However, we could not find any discussion in the draft RCD of the potential for health risks to adults who by occupation would be more likely to use DEET (e.g., park and forestry workers). Exposures in some classes of outdoor workers exceed the 7.5 applications per season used for the seasonal exposure estimate. A complete exposure and risk assessment would include consideration of the expected high-end exposures in this group.

Human Exposure Assessment (Sanborn, 1999)

This document contains essential elements pertinent to the draft RCD. We have read the human exposure assessment as well as documents relating to exposure assessment published by Selim (1991a,b; 1992) and Boomsma and Parthasarathy (1990) and have the following comments.

We have observed previously that upper-bound exposure estimates need to be included for all time and exposure scenarios. The minimal consideration of variability in uses of DEET, including the use of high-concentration products, fails to address the potential for over-exposure to DEET. In consideration of the available data, it should be noted that the study of Boomsma and Parthasarathy (1990) does not specifically state whether participants counted re-applications in a day as individual applications or as one collective application. However, this publication does provide some data (Table 50) on which to base estimates of high-end exposures. It appears, for example, that about 8 percent of adult men and 5 percent of children of the ages 12 and under applied more DEET to their skin in a single application (greater than 3 grams) than assumed for the high-end acute exposure estimates in the draft RCD (page 60, Table 20). The estimate of total seasonal use included in the draft RCD is only about twice these single high-end exposures, with no estimate of variability or distribution of uses. The draft RCD therefore does not address the use patterns that have resulted in the known toxic events.

We recommend that estimates of high-end seasonal exposures be included for both children and occupational use patterns. These estimates might have to be based on exposure scenario assumptions if no further data are available. Such scenarios might include a summer vacation in a mosquito area for children, based on average vacation length. An occupational scenario might include one month of exposure at the rates of DEET usage observed in the Florida Everglades (Sanborn, 1999, page 18). The resulting MOEs will be much lower than presently stated in the draft RCD.

C. Risk Characterization

The derived MOEs for various populations were presented. The lowest MOE for acute systemic effects was 83, for children less than 12 years old. The lowest MOE for local effects (dermal irritation) was 14 for children under a high use acute exposure. If our recommendations for NOAEL selections were adopted, the MOEs would be lower.

It is not clear how the acute dermal irritation MOE was calculated from the NOAEL, which was provided only in terms of mg/cm^2. Inclusion of the calculation and assumptions used would be helpful.

IV. Risk Appraisal

The uncertainties and limitations associated with this risk assessment are not adequately addressed in this section, particularly with respect to exposure-derived uncertainties. There is no separate section addressing scientific uncertainties as has been included in recent documents. If our recommendation for more discussion of upper-end exposures is followed (particularly

regarding occupational exposures), the uncertainties in these estimates should be addressed in this section.

The following comment relates to the statement on page 64 that "Data from the usage survey indicate that children less than 12 years old receive as much DEET per application as [an] adult male on average regardless of the difference in their body weight or surface area. Since this seems illogical, exposure estimates for adult females, juveniles (ages 12-17), and children (less than 12 years old) were also estimated by adjusting the adult male dermal dosage...." In the Boomsma and Parthasarathy study (1990), it was clear that juveniles under 12 were more likely to be sprayed with DEET by a parent. It was reported that parents were prone to over-apply DEET to their children. The data are from real applications and should not be dismissed or discounted. Therefore, we recommend that this alternate exposure estimation be dropped from the draft RCD and from the separate exposure assessment document.

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