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THE PRESENT SAFETY ASSESSMENT OF DEET

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ABSTRACT. Deet is considered to be the best "all around" insect repellent ever developed and is the most widely used insect repellent in the world. Since its first use in a consumer product in 1956, billions of applications have been made to human skin. Information about the safety of deet comes from the human clinical literature, animal toxicology studies, and poison control centers' experiences with deet. The clinical literature reports the association of deet with neurotoxicity in 14 individuals. Three of the cases resulted in death, whereas all of the other patients completely recovered. The exact role of deet in the toxicity reported is difficult to determine from the reports. Recently reported animal safety studies have examined potential neurotoxicity following multigenerational dosing. Effects on the nervous system were only seen when generalized toxicity was also observed. Thus deet is not a selective neurotoxin. Important information about deet also comes from an investigation into the reports of adverse affects reported to 71 poison control centers in the USA. An important conclusion from this study is that there is no evidence that increasing deet concentration has any effect on the severity of the symptoms reported. The vast majority of reported cases had either no symptoms or ones that resolved rapidly. In conclusion, a thorough examination of all information available indicates that the risk of serious adverse effects following the use of deet is extremely low.

INTRODUCTION

Our task is to provide some insight into the future role of repellents and give an overview of the status of deet. Clearly, repellents will be viewed as a critical public health tool in the years to come. In fact, as environmental concerns make the treatment of wetlands for mosquito control more problematic, personal repellents may remain as one of the few public health management tools acceptable to all. Repellents are also increasingly important given the seriousness of the Lyme disease situation. Lyme disease is currently the most common vector-borne disease in the USA, with more than 40,000 cases reported between 1982 and 1991 (Steere 1994). Reducing the risk of getting Lyme disease is primarily limited to the wearing of long clothing (often impractical in summer) and the use of a repellent. Deet is the most widely available and most effective repellent available for use on skin.

Since the introduction of deet in consumer products in 1956, literally billions of applications to human skin have been made, yet questions about the safety of deet persist to this day. Given this, we feel that it would be useful to provide an update on what we know about the safety of this compound.

Three main sources are available for information about the safety of deet: case reports of adverse effects in the clinical literature, animal toxicological studies, and the experience of poison control centers with respect to deet. By considering such evidence, one can make a reasonable assessment of deet safety.

CASE REPORTS OF HUMAN REACTIONS

Over the past 35 years, reports have appeared in the medical literature that discuss possible human health effects from the use of deet (Gryboski et al. 1961, Zadikoff 1979, Heick et al. 1980, deGarbino and Laborde 1983, Roland et al. 1985, Edwards and Johnson 1987, Oransky et al. 1989, Oransky 1991, Lipscomb et al. 1992). It is these cases that deal specifically with allegations of neurotoxicity that form the basis for most of the concern about deet safety. In Table 1 we present a compilation of the publicly available reports associating deet with neurotoxicity. Deet has been associated with toxicity of the central nervous system (more properly referred to as encephalopathy) in 14 individuals. Both males and females were equally represented in the reports. The deet concentration of the products used is known for 8 of the patients; 6 of 8 were products with less than, or equal to, 20% deet. Encephalopathy was seen more in young people than in adults; 13 of 14 of the cases were in children age 8 or under. The most common symptoms observed were convulsions and seizures. The case reported by Heick et al. (1980) involved lethargy and mood alterations, but no convulsions. Three of the 14 cases resulted in deaths; all the other patients recovered completely.

It is difficult from the papers to estimate the doses of deet that the people received. However, for 6 of the 10 cases, for which some mention was made of dose, it appears that heavy applications of deet preceded the development of the

encephalopathies. For 6 of the incidents referred to in 2 separate reports, essentially no clinical details were provided (Oransky et al. 1989, Oransky 1991). Although it is virtually impossible to determine the role of deet from these reports, we have nevertheless included for completeness the 6 individual cases that these 2 reports detail.

The whole issue of encephalopathy is problematic, especially with children. Although most cases are associated with viral infections, it is often difficult to assign a cause. The incidence of childhood encephalopathy peaks at 1–2 per 1,000 during the first 6 months of life (Wang and Bortolussi 1981) and declines slightly until after age 10 years. Koskiniemi et al. (1991) studied 405 children aged 1 month to 16 years that were treated for acute encephalopathy and concluded that respiratory viruses and varicella-zoster virus were the predominant causes for children ages 1–9 years.

Determining the cause of the encephalopathy is extremely difficult and requires early investigation (Kennedy et al. 1986). Although in some cases a superficial examination for infectious causes was done, only through a comprehensive evaluation can such causes by ruled out. It is therefore possible that several of the cases reported to be associated with deet may have been caused by infectious agents. The importance of a thorough investigation comes from the work of Kennedy et al. (1986), who examined 29 children and 3 adults that had encephalopathies in which the initial investigation failed to reveal an infectious cause (insect repellent use was not a consideration in these cases). Extensive viral serology and the quantitation of interferon in both the cerebrospinal fluid and serum revealed an active viral infection in 25 of 29 patients (noninfectious causes were identified in 3 of the patients).

In conclusion, the human clinical literature does contain a few reports of a temporal association between the use of deet and neurological signs. However, it is difficult to rule out other causes of the neurological signs seen and to establish a clear cause-and-effect relationship. Furthermore, the number of reports is small considering that between 50 and 100 million Americans use deet-containing insect repellents annually (USEPA 1980).

Table 1. Compilation of reports of neurological effects associated with deet.

Authors	Number of patients	Sex–age	% deet	Use pattern	Symptoms–diagnosis	Outcome
Edwards and Johnson (1987)	1	F–18.5 months	20	Frequent, child licked skin	Weakness, tremors, ataxia–encephalopathy	Fully recovered
deGarbino and Laborde (1983)	1	F–17 months	20	"Frequent" for 3	Encephalopathy	Death
Gryboski et al. (1961)	1	F–3.5 years	15	Heavy	Convulsions–encephalopathy	Fully recovered
Heick et al. (1980)	1	F–6 years	15	Heavy	Ataxia, lethargy–encephalopathy	Death after 8 days
Lipscomb et al. (1992)	1	M–5 years	First–95, then unknown	Two applications same day all over	Convulsion–encephalopathy	Fully recovered
Roland et al. (1985)	1	F–8 years	15, 100	Heavy	Seizures–encephalopathy	Fully recovered
Oransky et al. (1989)	5	M–3–7, 29 years	unknown	Not provided	Seizures–encephalopathy	Fully recovered
Oransky (1991)	1	M–8 years	unknown	Sprayed on carpet	Convulsion	Fully recovered
Zadikoff (1979)	1	F–5 years	10	Heavy	Convulsions	Death after 24 days
	1	F–18 months	10	Ingestion	Irritable, bizarre movements	Fully recovered

ANIMAL TOXICOLOGY STUDIES

The U.S. Environmental Protection Agency (USEPA) issued a Reregistration Standard for deet in 1980 that outlined a long list of studies that needed to be conducted to ensure the continued availability of deet (USEPA 1980). More

Table 2. Studies conducted by the Deet Joint Venture Group to support USEPA reregistration.

Mammalian Toxicology Studies

1. Rat 90-Day Dermal
2. Castrated Male Rat 90-Day Dermal
3. Micropig 2-Week Dermal Dose Range-Finding
4. Micropig 90-Day Dermal
5. Rat 90-Day Multistrain Renal Toxicity
6. Rat Acute Neurotoxicity
7. Rat Subchronic Neurotoxicity
8. Mouse 90-Day Dose Range-Finding
9. Mouse 18 Month Chronic Toxicity/Oncogenicity
10. Dog 2-Week Diet Palatability
11. Dog 3-Week Toxicity
12. Dog 8-Week Dietary Dose Range-Finding
13. Dog 8-Week Oral Gelatin Capsule Dose Range-Finding (Second Study)
14. Dog One-Year Chronic Toxicity
15. Rat Teratology Dose Range-Finding
16. Rat Teratology
17. Rabbit Teratology Dose Range-Finding
18. Rabbit Teratology
19. Rat 90-Day Dose Range-Finding
20. Rat Chronic Toxicity/Oncogenicity
21. Rat Two-Generation Reproduction
22. Hamster 2-Week Dose Range-Finding
23. Hamster 90-Day Dose Range-Finding
24. Determination of Expired Volatiles Following Oral and Dermal Administration in Rats
25. Pharmacokinetic and Comparative Dermal Absorption in Rats
26. Human Dermal Absorption

Mutagenicity Studies

1. Ames Test
2. Chromosome Aberrations
3. Unscheduled DNA Synthesis

Ecotoxicology Studies

1. Daphnid Acute Toxicity
2. Bobwhite Quail Acute Oral Toxicity

than 20 studies have been conducted on deet as a part of this program (Table 2). Studies have focused on the critical endpoints essential to the safety assessment of any molecule: acute, subchronic, and chronic toxicity; developmental toxicity (Schoenig et al. 1994); reproductive toxicity; mutagenicity; neurotoxicity (Schoenig et al. 1993); and oncogenicity. In addition, animal and human percutaneous absorption have been extensively studied. We will comment on 2 areas of particular interest: neurotoxicology and percutaneous absorption.

Because of the public concern about neurotoxicity, special efforts were made to examine potential neurotoxicity. The most thorough evaluation was conducted as part of a 2-generation reproductive study conducted in rats (Schoenig et al. 1993). Both sexes of the parental generation (F_0) received up to 5,000 ppm deet in the diet (the maximum tolerated dose) continuously through breeding, pregnancy, and birth of their offspring (the F_1 generation). The F_1 pups (both sexes) continued to receive deet up through sexual maturity and breeding, pregnancy, and birth of the F_2 generation. These rats, the 3rd generation, also received deet daily through the time that neurological evaluations were done on them (about 9 months of age). Of the many neurological tests run, the only potentially treatment-related finding was a slight increase in exploratory locomotor activity in the high-dose animals. Extensive histopathologic examination of central and peripheral nervous tissue failed to reveal any changes of toxicologic importance. From these data, it is important to note that effects on the nervous system occurred only when the dose was such that generalized toxicity also occurred. Thus, deet is not a specific neurotoxin. Moreover, doses that might cause toxicity, including neurotoxicity are much higher than a human would receive following normal use of deet.

Another important area of concern with deet has been its ability to penetrate the skin. Estimates of the percutaneous absorption for deet have varied widely from 7.9 to 59% depending upon the species tested and the conditions of the study (Feldman and Maibach 1970, Markina and Yatsenko 1971, Bloomquist and Thorsell 1977, Reifenrath et al. 1981, Robbins and Cherniack 1986). Each of these studies has limitations (such as low numbers of subjects) that affect their utility in determining the percutaneous absorption expected in humans.

The definitive study on the human absorption, metabolism, and excretion of deet has recently been completed (Selim et al. 1995). Adult male subjects were dosed topically with radiolabeled deet and housed in a clinic for 5 days. The deet was allowed to remain on the skin for 8 h before rinsing. Skin stripping of the application sites was done with cellophane tape to collect any deet remaining in the *stratum corneum*. Periodic blood samples were taken. Urine and feces were collected for the duration of the study. Radioactivity was determined in all samples. An excellent mass balance was obtained; fully 94.3% of the applied radioactivity was accounted for in the study with 100% deet. This is an outstanding recovery in a study of this type.

As determined by plasma radioactivity, the absorption of deet occurred quickly (within 2 h)

after application of the dose. Elimination of radioactivity from plasma was also swift. Quantifiable levels of radioactivity were detected in the plasma for only 4 h after the end of the 8-h exposure period. The vast majority of the deet that was absorbed was excreted in the urine. The mean total absorption was only 5.6% ($n = 6$) for undiluted deet and was 8.4% ($n = 6$) for deet in a 15% solution in ethanol. This is much less than occurs in experimental animals and less than previous estimates of human absorption.

HUMAN USE EXPERIENCE— THE POISON CONTROL CENTER DATA

Although clinical reports have appeared from time to time as discussed previously, until recently, no systematic large-scale study of adverse effects in humans has been reported. However, an investigation was published in 1994 that examined cases of adverse effects from exposure to deet-containing insect repellents reported to 71 poison control centers (PCCs) participating in the American Association of Poison Control Centers' National Data Collection System from 1985 to 1989 (Veltri et al. 1994). During this time, PCCs reported 9,086 cases of exposure to one of 56 products containing deet insect repellents. The participating centers covered a broad area of the United States with a population of more than 180 million people.

Although not without limitations, this is a very useful database to examine. Trained poison control specialists not only answer the initial call, but they follow-up with the caller until the case is resolved. At the conclusion of the case the poison information specialist assesses the medical outcome of the exposure according to criteria of severity (minor, moderate, major).

Most of the exposures reported to PCCs involved young children who usually had some oral contact with the product. Although 6,724 of the reports, spanning 5 years, involved the exposure of children under 6 years old, this number is not unexpected for commonly used consumer products. As a comparison, the PCCs received 10,789 reports of exposure of young children to laundry detergents and 16,169 calls due to exposure to household bleaches in 1989 alone (Litovitz et al. 1990). Older children, adolescents, and adults make up about 25% of the deet cases and they most frequently contact a PCC because the product has been sprayed in the eyes or inhaled.

More than half (54.0%) of the callers had no symptoms at the time of calling. Only 4 of every 10 patients (39.8%) had symptoms that were thought to be related to exposure. Symptoms were most likely to occur if the patient sprayed the product in the eye(s) or inhaled it, and least likely to occur if the patient ingested the product. Persons who got the product in their eyes or inhaled it were most likely to have a minor effect, whereas patients who ingested the product were least likely to have any effect at all. Sixty-six patients (about 1% of those with a definitive outcome) experienced moderate symptoms that were more pronounced or prolonged, but they resolved without life-threatening symptoms or permanent effects. Only 5 patients were reported to have experienced major effects from the exposure and one patient died 9 days after intentionally drinking 8 ounces of a deet-containing insect repellent.

One important point from the study is that there does not appear to be any evidence that increasing concentration of deet has an effect on the severity of symptoms following an exposure. Those few patients experiencing a major effect, and the case resulting in the death, involved products containing 11–50% concentrations of deet. It is apparent from this study that the risk of serious medical effects (including encephalopathy) following the normal use of deet-containing insect repellents is quite low.

CONCLUSION

An assessment of deet safety needs to consider all the evidence available: the human clinical reports, the extensive animal toxicological data, and information about the safety record of deet in actual use as collected from the poison control centers. Our evaluation of the record is that deet can be used with the confidence that the risk of serious adverse effects is very low.

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