UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PESTICIDE PROGRAMS
INSECTICIDE BRANCH

JUL 21 1999

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MEMORANDUM:

To: Julie Spagnoli, Bayer Corporation

From: Kevin Sweeney, Entomologist, RD

Date: July 22, 1999

Subject: Efficacy data supporting the registration of KBR-3023, EPA File Symbol 3125-LRE

I have reviewed those efficacy studies submitted in 86-5 format. Attached, please find two reviews on the submitted studies. Since the studies accompanying the letter from Heinrich Wolfers, dated April 14, 1999, were not submitted to front-end processing, were not in 86-5 format, and have not been assigned an MRID number by the Agency, I can not review them. I have perused these studies but can not complete an efficacy review for the file of the subject product until they have an MRID number. If you wish these studies to be considered as part of the registration decision, please format them accordingly and submit them to front-end processing.

As a result of the above, I have not included a summary of my product performance reviews. I will do so immediately if you do not submit the April 14, 1999 package for review, otherwise, I will wait until all data are reviewed. Based on the data reviewed to date, KBR 3023 provides a minimum protection time of 6 hours based on all pests evaluated.

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EFFICACY STUDY REVIEW FOR NEW CHEMICAL SUBMISSION

by

Kevin J. Sweeney, Entomologist
Insecticide Branch

Active Ingredient:
KBR 3023 - Propidine (1-Methylpropyl 2-(2-hydroxyethyl)-1-piperidine carboxylate

Activity: Arthropod Repellent

Registrant: Bayer **Contact Person**: Julie Spagnoli

EPA File No.: 3125-LRE **Product Name:** KBR 3023 Technical (96.8% propidine)

3125-LRR **Product Name:** KBR 3023 All-Family Insect Repellent Spray (20% propidine)

3125-LRN **Product Name:** KBR 3023 All-Family Insect Repellent Cream (20% propidine)

Background:

Bayer Corporation developed KBR 3023 as a repellent against blood-feeding arthropods including flies (Insecta: Order Diptera), mites and ticks (Arachnida: Order Acarina) and fleas (Insecta: Order Siphonaptera). The company is marketing this product as a DEET alternative and all submitted efficacy data used DEET as the standard for comparison. KBR 3023 is applied to the skin as a spray or cream. The company claims that KBR 3023 evaporates from the skin into the air forming a layer of scent. This layer interferes with the blood seeking arthropod's attractant mechanisms. In other words, the scent camouflages the attractants (carbon dioxide and lactate) emitted by the human host and the arthropod cannot find this host because it cannot smell it. Another theory is that the repellent affects the function of the olfactory sensory neurons resulting in their inability to smell the odors. Either effect has the same result.

These studies bring to light the repellent activity or enhancement of repellent activity by inert ingredients. Bayer has added [redacted] to its insect spray formulation. Testing was conducted in Malaysia with this compound against the mosquito, *Aedes aegypti*. They mixed it with DEET and KBR 3023 and it appears to enhance the effectiveness of these compounds.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

OVERVIEW:

The data submitted by Bayer resurrects the issue of repellent evaluations. This data does not conform completely to the EPA or Canadian requirements but appears acceptable to the World Health Organization. Testing was not done on all pests on the label. The company submitted no flea, tabanid fly, or "no-see-ums" data but put these pests on the label. The submitted data supports the labeling for mosquitoes, ticks, the stable fly, *Stomoxys calcitrans*, and the black fly, *Simulium spp.* For the company to include "biting flies" on the label, they should conduct a field test with tabanids. Field tests should also be done to include "no-see-ums" on the label.

Submitted Study: Animal Efficacy Testing of KBR 3023 MRID 444087-44.

Animal tests were done on the guinea pig and the results show the repellent activity of KBR 3023. Repellency tests were done with three mosquito species, *Aedes aegypti, Culex quinquefasciatus and Anopheles stephensi*, and the stable fly, *Stomoxys calcitrans*. The standard for comparison was DEET and they calculated repellency factors to qualify the differences in performance between DEET and KBR 3023. A 3% KBR 3023 solution was evaluated in the mosquito tests. They tested a 5% KBR 3023 against the stable fly. The repellent was considered effective if the mosquitoes bit the animal less than five times in five minutes. They continued tests every hour until the product lost its effect (> 5 bites in five minutes). The results showed that KBR 3023 repelled the tested mosquitoes and the stable fly.

Submitted Study: Human Efficacy Cage Testing of KBR 3023 MRID 444267-04

Material & Methods: They tested KBR 3023 against the mosquito, *Aedes aegypti*, the American dog tick, *Dermacentor variabilis*, and the stable fly, *Stomoxys calcitrans*. The criterion for assessing repellency was different from the animal testing protocol above. In addition, the criteria were different for each contractor. For the mosquito tests done by Professor Yap, they exposed the arm for five minutes every hour. If the number of bites exceeded three per five-minute interval, the product was no longer effective. For the experiments done by Hazelton Labs, they exposed the arm of the human volunteer for three minutes. If the number of bites exceeded four per three-minute test period, the product was no longer effective. They identified the third contractor only as SCJ (S.C. Johnson? Location unknown). For the SCJ mosquito tests, they exposed the arm for one minute every 30 minutes. If a bite occurred during two consecutive exposures, they ended the test. They applied these criteria to their tests with the stable fly too.

SCJ also did tests with the American dog tick. These tests used a three minute exposure at treatment times of 30, 60, 120 and 180 minutes from the time of initial exposure. The number of touches with the legs or mounts with all eight legs were recorded.

Results: The cage tests showed that KBR 3023 repelled mosquitoes, stable flies and the American dog tick. Only one mosquito species, *Aedes aegypti*, was tested in the human cage tests compared to four mosquito species tested in the guinea pig experiments. The EPA DEET standard requires no bites for the first two hours of testing with mosquitoes. The registrant's cage

tests do not show this result due to differences in exposure times and criteria used to assess efficacy. As a result, they did not establish the length of time this repellent works on mosquitoes in human cage tests.

Section G protocols require a minimum of one hour repellency for ticks. The only set of data submitted showed KBR 3023 surpassed this threshold value and repelled American dog ticks.

Submitted Study: Human Efficacy Field Trials of KBR 3023

The field trials were conducted with species of mosquitoes from the genera *Aedes, Culex, Mansonia,* and *Armigeres spp.* Human hosts bared both hands and legs, one hand and leg was the "untreated control" and the other hand and leg was the "treatment" with the respective repellent formulation. They repeated the experiments three times at each site. The time the field exposure took place coincided with the peak biting activity for each species. Tests done by SCJ were similar to the above but no control was used or if used, the data were not presented in this study.

[redacted]

Results: KBR 3023 showed excellent repellency against mosquitoes in all field tests. It was equal or to better than DEET. The repellency against ticks was also good but since they tested only one species, they need to collect more data for ticks

Conclusions & Recommendations:

The new repellent KBR 3023 showed good to excellent results against ticks, the stable fly, the black fly and mosquitoes. The results of the field and cage tests did not concur in all instances, especially for the mosquitoes. The field mosquito data appeared more consistent when compared with the laboratory cage tests and KBR 3023 was more effective in the field than in the lab. I recommend the following additional efficacy requirements for registration:

1. They must conduct cage testing for fleas with humans or they must remove this claim from the label.

2. They must conduct tabanid fly and "no-see-ums" field efficacy studies or the registrant will remove "no-see-ums" and "biting flies" from the label.

3. They must qualify the submitted human cage test data because cage testing is the best means of determining the length of protection time. The submitted data does not show a consistent protection time. More human cage tests with mosquitoes should be done using the same species evaluated in the guinea pig tests. The protocol should be the same for all species tested, no matter what contractor or laboratory is used. I recommend the registrant include all raw data sheets with each future submission.

4. The guinea pig appears helpful for establishing a test dose for humans but the data collected for mosquitoes with guinea pigs does not support the registration of this repellent.

5. Field tests with the end-use products 3125-LRR and 3125-LRN must be conducted. The formulations of these products are different. One product contains [redacted] while the other does not. The Agency must know if both products are efficacious in the field. FIFRA requires this data.

Additional Comments: INERT INGREDIENT INFORMATION IS NOT INCLUDED

KBR 3023 must conform to the same standards as those required of DEET:

a. Time to first bite is one of the most important criteria for establishing repellency. The usual index of efficacy is complete protection time (CPT) (ASTM 1992), which is defined as the time from application of the repellent to the first confirmed bite (a bite followed another within 30 minutes). The DEET standard requires a minimum CPT of two hours. Human cage tests with KBR must show equivalent efficacy. This does not mean that the trends shown in the human cage tests are not useful but the compound should be evaluated as required for DEET.

REFERENCES CITED

Anonymous. 1992. E 989-83 - Standard Test Method of Field Testing Topical Applications of Compounds as Repellents for Medically Important and Pest Arthropods (Including Insects, Ticks and Mites): 1. Mosquitoes. pp. 580-583 in Annual Book of ASTM Standards. Vol. 11.04. American Society for Testing and Materials, Philadelphia, PA., 1426 pp.

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MRID 447289-01

Title: Efficacy Data for KBR 3023: Mosquitoes, deer ticks, tabanids, cat fleas

non-GLP studies

OVERVIEW:

These studies were submitted in addition to the original Bayer AG efficacy data that accompanied the submission of this new chemical. In the present submission, protection times were recorded based on mean time to first bite for each pest. The data for fleas and tabanids were requested by the Agency to support label claims to repel these pests on the end use product labels.

Title: Evaluation of two repellent formulations against the yellow-fever mosquito, *Aedes aegypti,* in Puerto Rico by Pest Management International - Carlos Rosario.

A 20% KBR lotion was tested in this study and compared to a 20% DEET lotion on the legs of three volunteers. One volunteer was the negative control subject and the other two served as the treated subjects. The test was conducted over three days, a different person served as the negative control each day. Field collected *Aedes aegypti* mosquitoes were used. The test site was an enclosed room into which an undetermined number of mosquitoes were released.

The 20% KBR treatment provided 6 hours of protection against mosquito bites.

Title: Evaluation of a personal repellent against ticks. Lab study conducted by ICR in Baltimore, Maryland under the direction of Robin Todd.

The method used in this study was the standard ICR protocol, the "Que-tip test" for ticks. In brief, this method is controversial but entails a repellency evaluation based on a tick not leaving a Que-tip held directly above a treated area of the skin for 30 seconds or if a tick drops onto the skin, it falls off after 15 seconds. Based on this method, KBR exhibited repellency for 2.5 hrs.

Title: Study about the comparative testing of different repellent formulations against tabanids in the field by Prof. Muhlhofer of the Labor fur Hygiene und Sicherheit, Austria.

This was a field test conducted in an unknown location in Austria. The test insects were flies from the family Tabanidae including *Tabanus bovinus, Haematopota pluvialis, Chrysops relictus*.. The stable fly, *Stomoxys calcitrans*, was also tested. KBR was evaluated as a 7.5% lotion applied to 100 sq.cm of skin surface and compared to a 10% DEET lotion. Five volunteers were assigned to each treatment group and exposed for 30 minutes per hour. The study discusses the use of high, medium , and low densities but each level is undefined. The test ended with the first bite. Therefore, the results show that both DEET and KBR repel these flies for short periods

of time, less than three hours. This test supports the placement of these flies on the label but did not provide a valid protection time.

Title: Efficacy of KBR 3023 in comparison to DEET on human arms against the cat flea, *Ctenocephalides felis by Bayer AG*

This study employed a new and unconventional method of performing flea repellency evaluations. Small transparent boxes were used into which five adult cat fleas were placed. Two volunteers were used in this test. There was no negative control. On 90 sq. cm of each arm was placed 150 ul of 20% KBR lotion or 20% DEET lotion. The cage was fastened to the arm and the arm exposed to the fleas for three minutes/hr. for nine hours. The repellent failed if more than two bites occurred in three minutes. According to the test criteria the arm was protected by both repellents for nine hours. However, the KBR treatment received a bite at six hours and again at nine hours. No bites were received in the DEET treatment.

The flea data was very limited in scope of evaluating protection and another study will be required to list a protection time on the label.

The above studies show that KBR can repel the above tested pests and they can remain on the label. However, more work will need to be done to determine protection times against the listed pests. This work should be required as a condition of the registration and the methods and standards used must conform to the new testing and labeling guidance for repellents that is in preparation.

PICARIDIN / KBR-3023 7-21-99

Page _____ is not included in this copy.

Pages 9 through 11 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

X Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.