EFFICACY REVIEW

DATE: IN12- 4-95 OUT 3-21-96

FILE OR REG. NO. None

PETITION OR EXP. PERMIT NO.

DATE DIV. RECEIVED December 4, 1995 and March 7, 1996

DATE OF SUBMISSION December 1, 1995 and March 7, 1996

DATE SUBMISSION ACCEPTED

TYPE PRODUCT(S): (I,)D, H, F, N, R, S Repellent

DATA ACCESSION NO(S). None; D221373; S497724; Case# 287198; AC:400

PRODUCT MGR. NO. 10-Keigwin/Keigwin

PRODUCT NAME(S) KBR 9023

COMPANY NAME Bayer Corporation, Agriculture Division

SUBMISSION PURPOSE Provide performance data not requested by the Agency comparing efficacy and duration of a new chemical repellent candidate to a deet standard.

CHEMICAL & FORMULATION 1-Piperidinecarboxylic acid, 2-(2-hydroxyethyl), 1-methylpropyl ester 100.0%
(Dilutable liquid of unspecified Sp. Gr.)

CONCLUSIONS & RECOMMENDATIONS The data presented in the unaccessioned volume entitled "KBR 9023 Efficacy Data" were submitted by the applicant on their own initiative, not requested by the Agency. Because the development of a replacement chemical repellent for use on human skin to repel medically important arthropods (biting flies and mosquitoes, ticks, etc.) with equal or better results than currently obtained with deet (diethyl meta toluamide), is in the interests of EPA as well as a benefit to the developing company, the applicant has requested we review the submitted data to determine whether testing so far conducted is in conformance with the Product Performance Guidelines with respect to standards of effectiveness and duration of protection, as well as examining the testing conditions to ensure their meeting Agency requirements of procedures and validity of observations. Since the first of these objectives needed to be accomplished prior to the applicant's meeting with the Product Manager prior to application in a formal way, which meeting took place on or about the date(to be continued)

of February 23, 1996, we have previously examined the data in the volume denoted by D221373 in a preliminary manner and determined that submission of the data from testing conducted by S. C. Johnson and Son, which would not be available except in summary form until March 1996, was necessary for a final decision regarding the acceptability of testing conducted thus far. Subsequent to the applicant's discussion with the Product Manager, and the date by which S. C. Johnson's test data would become contractually available to the developing company by prior agreement having passed, the applicant has recently submitted the remaining test data and the following review includes these results in making a determination.

The efficacy testing conducted using guinea pigs may be summarized as follows: KBR 9023 gave 2.4X duration of protection of deet against Aedes aegypti, 1.4X against Culex quinquefasciatus, 1X against Anopheles stephensi, 4.2X against Stomoxys calcitrans, in screening tests. The factors for these same species in blind comparisons subjected to statistical evaluation were similar: 2X, 1.8X, 2.4X and 3.9X, respectively.

The efficacy testing conducted using caged mosquitoes and exposed human skin may be summarized as follows: KBR 9023 gave 1.4 times the protection of deet against Ae. aegypti in the tests conducted by Yap in Malaysia, and the same factor in tests conducted by Hazelton Laboratories in the U. S. Results of S. C. Johnson's tests indicated a 3.2X factor in favor of deet against Ae. aegypti, but a 1.7X factor in favor of KBR 9023 against S. calcitrans. No ready explanation for the failure of KBR 9023 against caged Aedes mosquitoes is given, especially in light of results in field tests, to be discussed below. In a separate test, KBR 9023 gave essentially equal protection against touches by Dermacentor variabilis to deet for 120 minutes after treatment and against mounts by the same pest for 180 minutes, but significantly less protection against touches at 180 minutes than deet.

The efficacy testing conducted in the field may be summarized as follows: KBR 9023 gave numerically longer protection than deet against Aedes albimanus and Culex quinquefasciatus in Yap's tests conducted in Malaysia, with both chemicals exceeding the 8 hours that are considered complete protection by repellency in such circumstances. KBR 9023 gave equal protection to deet against mixed mosquito populations in Sixl's tests conducted in Austria and against the European castor bean tick, Ixodes ricinus, a vector of tick-borne encephalitis, in the tests conducted by the same researcher in the same country, with both chemicals providing more than 4 hours protection against ticks and from 2.5 to 4 hours vs. mosquitoes.

Field tests conducted by S. C. Johnson and Son in the U. S. have only recently become available, so their discussion has purposely been left until the last. In Racine County, Wisconsin tests conducted June to September 1990, KBR 9023 had numerically (but not significantly) longer protection time against Aedes spp. than deet. In a Florida Everglades test conducted in August 1990, KRB 9023 had numerically (but not significantly) longer biting protection against Aedes taeniorhynchus than did deet. In a Greenbush, Maine test conducted in June 1990, (to be continued)

deet had a numerically (but not significantly) longer biting protection time than did KBR 9023 against Aedes spp. In this case, however, there was a difference in first confirmed bite time of only about an hour compared to the nearly 3 hours in the previously discussed laboratory test. In the other test conducted in Greenbush, Maine, KBR 9023 had a significantly longer biting protection time against the black fly Simulium venustum than did deet.

Having completed the review of all of the raw data submitted by the applicant and the summarized data reported by S. C. Johnson and Son, we are ready to answer the specific questions asked by the applicant in their December 1, 1995 letter. Taking each in turn, 1) the current data are adequate to support claims for repellency against mosquitoes, biting flies and ticks for the subject chemical when used on exposed human skin at the same concentrations and similar directions as is currently found on deet labels; additional testing would be necessary to support claims for deer flies, horse flies and especially sand flies. No additional cage tests for mosquitoes are required at the present time, but additional field trials would be required for biting flies, particularly sand flies (punkies or no-see-ums), and would be desirable for greenheads or other deer fly species. Not required but recommended are additional field tests on Dermacentor spp. ticks since the only field tests reported on ticks thus far are with Ixodes ricinus. We also strongly recommend limited field tests or modified laboratory tests using either filter paper or human tests with another Ixodes sp. tick, either I. dammini, I. scapularis or I. pacificus, which are known Lyme disease vectors, in view of the medical significance of these pests in the U. S. 2) Yes, there are formal or specific requirements or guidelines for conducting these efficacy studies to be found in § 95-9(a) and (b)(1)(iii),(iv) and (v) on pp. 262-264 of the Product Performance Guidelines (for ticks, mosquitoes and biting flies) and in § 95-10(a) and (b)(1)(ii), (2)(ii) and (5)(ii) on pp. 264-266 of the Guidelines with respect to mosquitoes, black flies and biting midges (including sand flies). 3) The Agency does not have a list of institutions where testing was conducted which met guidelines/data requirements, but we have had many instances of acceptable data from such institutions as Harvard School of Public Health; USDA Insects Affecting Man and Animals Laboratory and University of Florida laboratory, both in Gainesville; Rutgers Medical Entomology Laboratory and several facilities in New York. 4) Provided initial claims on the label submitted at the time of application for registration reflect concentrations and amounts applied as previously tested and are limited to mosquitoes, black flies, stable fly and ticks, no additional data will be required prior to registration. In order to support claims for deer flies (particularly greenheads) and sand flies, additional data may be submitted later according to an agreed schedule. Furthermore, any claims for leeches would require additional data due to the unique nature of such pests, as would claims that the subject chemical is effective in repelling fleas require submission of flea data.

RL Vern L. McFarland, IRB