Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Re-evaluation Decision Document RRD2001-02

n-Octyl bicycloheptene dicarboximide (MGK Synergist 264)

The purpose of this document is to notify registrants, pesticide regulatory officials, and the Canadian public of the status of the re-evaluation of *n*-octyl bicycloheptene dicarboximide (MGK Synergist 264).

Registrants, pesticide regulatory officials, and other interested parties were notified in June 1990 by Announcement Document A90-01, Re-evaluation of Personal Insect Repellents, of the Pesticides Directorate, Agriculture Canada, that such repellents would be re-evaluated under Section 19 of the Pest Control Products (PCP) Regulations. The registrants of personal insect repellent products were asked to submit, within 6 months, indices to all known toxicology and efficacy studies on their products and copies for re-evaluation of any of the studies that had not already been submitted.

Eight active ingredients were named in Announcement Document A90-01, but only one is considered in this report, namely MGK Synergist 264 (*n*-octyl bicycloheptene dicarboximide) as used in personal insect repellents (the other uses of MGK Synergist 264, in insecticide products, are not currently under re-evaluation). Of the seven other active ingredients named in the announcement, three (citronyl, dimethyl phthalate, and ethyl hexanediol) are no longer registered, two (oil of citronella and oil of lavender) are still used in registered personal repellents and are being re-evaluated separately, and the re-evaluation of *N*,*N*-diethyl-meta-toluamide (DEET) and MGK Repellent 326 (di-*n*-propyl isocinchomeronate) is completed and will be discussed in separate documents.

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Risk Assessment

A full battery of studies (except for neurotoxicity studies) was submitted for re-evaluation. The Pest Management Regulatory Agency (PMRA) carried out the standard process of evaluating the studies and calculating potential exposure as a result of the use of products containing MGK 264. Initially, margins of exposure (MOEs) were calculated for MGK 264 alone, although MGK 264 is only registered in products as a mixture with DEET in concentrations ranging from 2 to 6%.

Because of the lack of neurotoxicity data for MGK 264 and the concerns about neurotoxicity in insect repellents, an MOE of 300 was targeted for MGK 264 instead of the standard MOE of 100. Based on the acute risk assessment, only products which contain 2% of MGK 264 would achieve the MOE of 300, but they would have to be restricted to adults only; all concentrations resulted in inadequate MOEs in the acute risk assessment for children, based on multiple applications. Intermediate-term MOEs were unacceptable for all populations (i.e., adults and children) at all concentrations.

Currently there are no insect repellents registered which contain MGK 264 alone as the active ingredient. MGK 264 is generally used as a synergist for and is co-formulated with DEET and MGK 326 in insect repellents. It is meant to slow down the detoxification of a chemical in the target species. It is not known, however, if and how MGK 264 enhances the repellency of DEET and MGK 326. MGK 264 is claimed to enhance the efficacy of DEET, i.e., to be a synergist, however, as its synergistic effects on DEET toxicity to humans are unknown, an MOE of 1000 is targeted for DEET when combine in an insect repellent with MGK 264. The extra 10-fold uncertainty factor for DEET is required due to lack of toxicity data that provide information on the potential interaction between DEET and MGK 264. The results of the DEET risk assessment did not show an MOE of 1000 or greater in any DEET insect repellent. Due to the potential synergistic effects on DEET in humans, the PMRA has concluded that MGK 264 should not be formulated with any DEET insect repellent until the safety of these combinations is ascertained. As indicated in the Regulatory Decision, steps have been taken to cause the marketing of these products to be terminated.

Efficacy Assessment of Mixtures of DEET, MGK Repellent 326, and MGK Synergist 264

As stated in Announcement Document A90-01, Re-evaluation of Personal Insect Repellents, one of the six factors in the decision to re-evaluate personal insect repellents was that “There is some uncertainty that all registered products are efficacious for the pests, uses and protection times claimed.” This led to the call for efficacy data and to a literature survey carried out by the PMRA.

Most of the efficacy data reviewed as a part of the re-evaluation of all of the personal insect repellents were gathered by treating the forearms or lower legs of test subjects with standard dosages of the repellent and exposing the treated areas continuously or intermittently to unfed insects in a cage or biting populations in the field. The usual index of efficacy has been the complete protection time (CPT), which is defined as the time from application of the repellent to

the first *confirmed* bite (a bite followed by another within 30 min). This is an appropriate index for end-use products because most users want *complete* protection rather than partial protection for a longer period.

Most laboratory tests used the yellow fever mosquito, *Aedes aegypti* (L.), or the stable fly, *Stomoxys calcitrans* (L.), reared under standard conditions and uniform in age and nutritional state. The repellents were applied at standardized dosages to human forearms, which were exposed to mosquitoes or stable flies in a test cage for a few minutes at 30-min intervals until bites were received at two consecutive exposures. The CPT was the time between treatment and the first confirmed bite.

In field tests against mosquitoes and other biting flies, the test surfaces were the bared forearms of each subject, from wrist to elbow, or the legs from ankle to knee, depending on the attack behaviour of the insects concerned.

In Table 1, the mean CPT values for mixtures of DEET, MGK Repellent 326, and MGK Synergist 264 against mosquitoes in one laboratory study and one field study at Ste.-Anne-de-Bellevue, Quebec, are compared with expected CPT values for solutions of DEET alone, at concentrations equivalent to DEET plus all the other actives combined in the mixtures and to the DEET only in the mixtures.

CPT values for 20% DEET + 4% MGK 264 against mosquitoes were shorter than those calculated for 24% and 20% DEET alone. Mixtures of DEET + MGK 326 + MGK 264 generally remained effective against mosquitoes for about as long as would be expected for equivalent concentrations of DEET alone. The products tested do not cover the full range of concentrations of actives in currently registered products, and there are not enough data to perform regression analyses or derive expected CPT values for the mixtures against mosquitoes.

No data were found to support the label claims of efficacy of these mixtures against other pests (black flies, biting midges, deer flies, stable flies, fleas, chiggers, and ticks).

Table 1 Complete protection times (CPTs) for mixtures of DEET with other active ingredients compared with those for equivalent dosages of DEET alone

	CPT (min)		
		Expected*	
Mixture	**Measured**	**DEET plus all other actives**	**DEET only**
Laboratory study, mosquitoes, *Aedes aegypti* (L.)			
11% DEET + 1% MGK 326 + 2% MGK 264	250	265	228
Field study, mosquitoes, *Aedes* spp.			
20% DEET + 4% MGK 264	247	346	319
7% DEET + 2% MGK 326 + 1% MGK 264	214	214	160
11% DEET + 1% MGK 326 + 2% MGK 264	277	265	228
25% DEET + 5% MGK 326 + 2% MGK 264	371	390	352

Conclusions

The PMRA has concluded that there is insufficient justification to maintain registration of mixtures of MGK 264 with DEET and with DEET and MGK 326. Due to the extra uncertainty factor which had to be added to account for the unknowns of the combination of MGK 264 with DEET, an adequate MOE cannot be achieved for the DEET. In addition, the data available do not show any consistent or significant gain in CPT against mosquitoes for the products with DEET + MGK 264 or with DEET + MGK 326 + MGK 264 compared with DEET alone at equivalent concentrations. Since the only reason to add MGK Synergist 264 would be to increase efficacy, there is no justification for continued registration of products containing MGK 264 based on the efficacy evaluation.

Regulatory Decision

In light of the conclusions outlined above, the registrant (McLaughlin, Gormley, King Company) of technical-grade MGK Synergist 264, and the manufacturing concentrates containing them, has discontinued sale and distribution of the technical active ingredient and the manufacturing concentrates for use in personal insect repellents, pursuant to Section 16 of the PCP Regulations.

The PMRA has notified registrants of end-use products of this decision and anticipates that registrants will request a voluntary discontinuation of the sales of their products containing MGK Synergist 264 for use in personal insect repellents, pursuant to Section 16 of the PCP Regulations. The effect of voluntary discontinuation would be that product could no longer be sold by registrants effective August 31, 2002. Under authority of Section 16 of the PCP Regulations, distribution and sale of product by other than the registrant would be permitted until December 31, 2002. Voluntary discontinuation of sales by a registrant is an alternative to the taking of action against the registration as a means of terminating the marketing of a product.

The decisions outlined in this Decision Document conclude the re-evaluation by the PMRA of the use of MGK Synergist 264 in personal insect repellent products.