5H5090 FOOD ADDITIVE PETITION BRW

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: August 12, 1976

SUBJECT: Application for new registration
Killmaster II, EPA #26693-E

FROM: Edwin R. Budd/Toxicology Branch
E Budd 8/17/76

TO: Frank Sanders/PM #12

SUMMARY:

1) See earlier reviews on this application (dated 5/6/76 and 5/25/76).
2) The toxicity data referenced by the applicant for the active ingredient, chlorpyrifos (technical), was found to be adequate and sufficient for the purpose of registration of the subject product (Killmaster II). Additional toxicity data on chlorpyrifos (technical) will not be required.
3) In addition to the acute toxicity studies already submitted for the formulated product, an acute inhalation LC-50 study (rats), a 21 day subacute dermal study (rabbits) and a 21 day subacute inhalation study (rats) must be submitted for the formulated product. Both subacute studies must include RBC and plasma cholinesterase activity determinations at appropriate intervals during the studies and at the termination of the studies.
4) Toxicology data on the other two active ingredients (aromatic petroleum derivative solvent and petroleum distillate) must be submitted or referenced. An alternative is to request of EPA that these two ingredients be allowed to be included under inert ingredients, in which case toxicology data on them will not be required.
5) Note required label changes which are specifically described under "Label Review" 1) and 2).
6) Note objection to the proposed use of this formulation within food handling establishments and deference to Chemistry Branch on this question (See "Label Review" 3)).

DISCUSSION:

REFERENCED DATA ON TECHNICAL PRODUCT

The toxicity data referenced by the applicant for the active ingredient, chlorpyrifos (technical), was found to be adequate and sufficient for the purpose of registration of the subject product (Killmaster II). Additional toxicity data on chlorpyrifos (technical) will not be required. The following is a brief summary of selected toxicity data on chlorpyrifos which was taken from a review by Dr. Parkin (dated 11/16/72) of data presented by Dow Chemical Company in P. P. 3F1306 (submitted 8/28/72).

Acute oral LD-50 (rats), Tech. = 82-245 mg/kg, Toxicity Category II
Acute dermal LD-50 (rabbits), Dursban 24E and Dursban 25W = 2830-3360 mg/kg, Toxicity Category III
Acute inhalation LC-50 (rats), Dursban 24E = greater than 5 mg/liter Toxicity Category III
Eye Irritation (rabbits), Tech.--slight redness at 7 days Toxicity Category II
(Repeated) skin irritation (rabbits), Tech.--slight hyperemia and burns Toxicity Category III (?)

Skin sensitization (guinea pigs)--negative

Subacute dermals
Subacute inhalations
Subacute orals
negligible systemic effects at doses causing significant decrease of cholinesterase activity

Cholinesterase activity (many studies; many routes; acute, subacute, chronic)
Chlorpyrifos is a potent cholinesterase inhibitor in rats, dogs, monkeys and other species. The cholinesterase NEL in 2 year dog feeding study was 4 ppm in diet!

Hen demyelinization test--single oral doses up to 150 mg/kg produced no delayed ataxia or paralysis up to 27 days (no histopathology).

Teratology study (in conjunction with reproduction study) (rats)
Doses up to 1.0 mg/kg in diet produced no toxic teratogenic or reproduction effects at this or lower doses.

Human studies--only signs of toxicity at several routes of administration and several doses used were dose-related cholinesterase inhibition.

Potentiation studies (rats)--chlorpyrifos, in combination with malathion (50:50) decreased the expected acute oral LD-50 approximately three fold (i.e. they potentiated!).

Antidotal study (calves)--atropine and/or 2-PAM did not appreciably influence the lethality of previously administered lethal doses of chlorpyrifos.

Chlorpyrifos appears to be a typical organophosphate pesticide. It is a potent cholinesterase inhibitor. The dietary NEL (dogs, 2 years) was 4 ppm. Systemic effects occur at about ten times the level causing decreased cholinesterase activity (rats). It potentiates with malathion. Typical antidotal treatments were relatively unsuccessful in decreasing lethality.

ADDITIONAL REQUIRED TOXICITY TESTS ON FORMULATED PRODUCT

In view of the aforementioned toxicological data on chlorpyrifos (especially its potent effect on cholinesterase inhibition, its capability to potentiate with other organophosphates and the lack of significantly effective antidotal treatment), Toxicology Branch is reluctant to approve the registration of the subject product, which contains a higher amount of chlorpyrifos (2%) than do other similarly used currently registered products (up to 1%), for the domestic applications proposed until full and adequate toxicity studies on the formulated product are submitted and the potential hazard to human health can be precisely evaluated. Accordingly, in addition to the acute toxicity studies already submitted, an acute inhalation LC-50 study (rats), a 21 day subacute dermal study (rabbits) and a 21 day subacute inhalation study (rats) must be submitted for the formulated product. Both subacute studies must include RBC and plasma cholinesterase activity determinations at appropriate intervals during the studies and at the termination of the studies.

ADDITIONAL REQUIRED TOXICITY TESTS ON OTHER ACTIVE INGREDIENTS

The submitted label for the subject product lists "aromatic petroleum derivative solvent" (1.2%) and "petroleum distillate" (94.7%) as active ingredients. Toxicology data on these two active ingredients must be submitted or referenced. An alternative is to request of EPA that these two ingredients be allowed to be included under inert ingredients, in which case toxicology data on them will not be required.

LABEL REVIEW

1) Delete present statement at top of front panel and replace with "Restricted Use Pesticide" at top of front panel--immediately followed by "For retail sale to and application only by Certified Applicators or persons under their direct supervision".
2) Immediately under "directions for use" (on left panel) insert "Restricted Use Pesticide".
3) The applicant includes as uses (on right panel) "applications within food handling establishments". The justification for this use is apparently the submitted copy of the Federal Register, vol. 41, no. 27 (February 9, 1976), 5631-2, in which the food additive chlorpyrifos was allowed to be applied in food handling establishments solely for spot and/or crack and crevice treatments. One condition of this use, however, is that the "spray concentration shall be limited to a maximum of 0.5% active ingredient". The concentration of active ingredient in the subject formulation (not a spray) is 2.0%. This proposed use for the subject formulation is apparently unlawful. Toxicology Branch defers to Chemistry Branch on this question. If such use is allowed, all inerts in the formulation will have to be cleared.