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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CASWELL FILE

DATE: September 10, 1979

SUBJECT: EPA File Symbol: 42693-R
FORMULA 1 (ONE) ROACH POWDER Caswell #108

FROM: B. T. Backus
IRB/TSS

TO: Mr. William Miller
Product Manager 16

Applicant: DAUD CHEMICAL CO.
334 Electra Drive
Houston, TX 77024

Active Ingredient:
Borax.....33%
Inactive Ingredients:.....67%

Background:

Among other things, the applicant does not wish to use the "Cite-All" method of support, objecting (letter of May 7, 1979) to offering payment for use of data.

Recommendations:

The applicant should be informed of the following, particularly in reference to his letter of May 7, 1979:

1. The Agency is working under legal constraints regarding its use of previously submitted data. The data within Agency files is still owned by the companies which submitted it. If we register a pesticide and the applicant has submitted neither the appropriate scientific studies on that formulation, nor an offer-to-pay compensation statement, then the Agency is legally liable for using this previously submitted data. A number of court decisions against the Agency have emphasized this point.

2. An applicant who is proposing to register a formulation which contains an already registered active ingredient can, if he does not wish to offer to pay compensation, contract with a scientific laboratory to generate the appropriate studies. As far as the toxicological requirements are concerned, these would be the following on the proposed formulation:

    a) Acute Oral LD50 (rat)
    b) Acute Dermal LD50 (rabbit)
    c) Eye Irritation (rabbit)
    d) Dermal Irritation (rabbit)

    The procedures should be those indicated in the Federal Register, Vol. 43, #163, August 22, 1978.

    These studies should be performed under the direction of personnel who have the education, training and experience appropriate for testing and evalu-

ation. A certified pathologist, or a person with equivalent training, with experience in laboratory animal pathology, should have the final responsibility for the accuracy and reliability of all diagnoses, conclusions, and reporting.

For the Oral LD50 study, the formulated product, as proposed for registration, should be used. Test subjects should be young male and female rats. If data based on testing with at least 10 animals (5 of each sex) are submitted showing that the LD50 is greater than 5 gm/kg body weight no further testing at other dose levels would be necessary. If mortality is produced, then the LD50 should be determined by testing at least 3 groups, with mortality between 10 and 90 percent. Animals should be observed at least 14 days after product administration; symptoms and time of mortality should be reported. Survivors should be sacrificed and subjected to a complete gross necropsy; all abnormalities should be reported. Animals should be weighed on day of dosage; at 7 days, and at 14 days or death.

The report should include a tabulation of response data by sex and dose level; LD50 for each sex (with method of calculation specified); 95% confidence interval for the LD50; and dose-response curve and slope.

For the Dermal LD50, the formulated product, as proposed for registration, should be used. If the test substance is a solid, it should be made into a paste with physiological saline before application. Test subjects should preferably be young adult male and female rabbits. If data based on testing with at least 10 animals (5 of each sex) with abraded skin are submitted showing that the LD50 is greater than 2 gm/kg body weight for the 24-hour contact period, no further testing at other dose levels would be necessary. Otherwise, at least 3 dosage levels, with mortality rates between 10 and 90%, should be used.

The application site should be free of hair on all animals. For abraded sites, the abrasions should be made in such a way as to penetrate the stratum corneum, but not the dermis. The test substance must be kept in contact with the skin of at least 10 percent of the rabbit body surface for at least 24 hours. The preferred application site is a band around the trunk of the animal. A wrapping material such as gauze covered by impervious, non-reactive rubberized or plastic material should be used to retard evaporation and keep the test substance in contact with the skin. At the end of the exposure period, the wrapping should be removed, and the skin wiped (but not washed) to remove any test substance still remaining. Animals should be observed 14 days. Any symptomology (including time of onset, nature, severity) should be reported, as well as mortality. The weight of each animal must be determined on the day of dosing, at one week, and at two weeks, or day of death.

All survivors should be sacrificed. All test animals (whether dying by sacrifice or as a result of exposure to the test material) should be subjected to a complete gross necropsy. All abnormalities should be reported.

The report should include a tabulation of response data by sex and dose levels, and whether or not (and if so, which) animals had abraded skin; LD50 for each sex (with method of calculation specified); 95% confidence interval for each LD50; and dose response curve and slope.

The Primary Eye Irritation study should be conducted using the product as proposed for registration. If it is a solid or granular product, it should be ground into a fine dust or powder. The test material should not be moistened before it is placed in the eye. Test subjects should be albino rabbits. At least nine animals should be used.

A dose of 100 milligrams of test material should be applied to one eye of each of the nine animals. It should be placed on the everted lid of one eye; the upper and lower lids should then be gently held together for 1 second before releasing to prevent loss of material. The other eye would be untreated, serving as a control. The treated eyes of six of the rabbits should remain unwashed; the remaining three would have their treated eyes flushed for one minute with lukewarm water starting no sooner than 20-30 seconds after instillation.

Readings of ocular lesions should be made at 24, 48, and 72 hours, and at 4 and 7 days after administration. Grading and scoring of irritation should be performed in accordance with Draize, J.H. et al. (1965) "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics - Dermal Toxicity," pp. 49-52. Association of Food and Drug Officials of the U.S.

The Primary Dermal Irritation study should use the formulated product as proposed for registration; the preferable subject species is the albino rabbit. At least 6 test subjects should be used. If the test substance is a solid, it should be slightly moistened with physiological saline before application. A dose of 0.5 gm of solid is to be applied to each application site.

The test substance should be introduced under 1 inch square gauze patches. The patches should be applied to two intact and two abraded skin sites on each animal. For all animals, the application sites should be clipped free of hair. In addition, the abrasion (for abraded sites) should penetrate the stratum corneum, but not the dermis. A wrapping material such as gauze covered by an impervious, nonreactive rubberized or plastic material should be used to retard evaporation and keep the test substance in contact with the skin for 24 hours. The animals should be restrained. At the end of the exposure period, the wrapping should be removed, and the skin wiped (but not washed) to remove any test substance still remaining.

Animals should be observed and signs of erythema and edema should be scored at 24 and 72 hours after application of the test substance. The irritation is to be scored according to the technique of Draize, J.H. (1959) "The Appraisal of Chemicals in Foods, Drugs and Cosmetics," pp. 36-45. Association of Food and Drug Officials of the United States, Austin, Texas.

The report should include, in tabular form, scores for erythema and edema for each individual test animal at 24 and 72 hours, and the primary skin irritation scores according to the technique of Draize.

If there are any questions regarding these protocols, the applicant should refer to the Federal Register, Vol. 43, #163, August 22, 1978. The protocol for the Oral LD50 study is given on pages 37355-37356; for the Dermal LD50 study on pages 37356-37357; for the Primary Eye Irritation study on pages 37359-37360; and for the Dermal Irritation study on pages 37360-37361.

3. One advantage to having these studies done would be that, although placed on file within the Agency, the applicant would retain ownership. He would have the right to ask compensation from applicants using the "Cite-all" method of support for identical or similar formulations.

4. The "Cite-all" method of support was initiated to expedite and reduce the cost of the registration process, particularly for smaller companies. The process of contracting for, and obtaining acute short-term toxicological studies is time-consuming (several months, at least) and comparatively expensive (estimated $2000-$3500) for a small business. In the "Cite-all" method the applicant, by communicating directly with the owners of the data, is able to determine what the cost (if any) of data compensation would be.

5. We must express concern over the terminology "nebulous information" (letter of May 7, 1979). The Agency has to make responsible decisions on the basis of studies which show the potential hazards associated with possible exposure to a pesticide. Depending on the results of these studies, the Agency determines whether or not the potential benefits outweigh the risks, assigns the label signal word (DANGER; WARNING; or CAUTION) and prescribes precautionary and first aid statements for the label.

6. Regarding the toxicity of borax the following is an excerpt from a current volume (Gosselin, Hodge, Smith and Gleason, Clinical Toxicology of Commercial Products, 4th edition, the Williams & Wilkins Co, Baltimore, 1976: Section III, pp. 63-66):

> The reputation of borates is so firmly entrenched that they are still readily available despite toxic potentialities reported as early as 1883. Acute poisonings have followed ingestion, parenteral injection, enemas, lavage of serous cavities, and application of powders and ointments to burned and abraded skin. Ironically, many of these incidents have occurred in hospitals through ignorance or error.

The Agency has registered, and will continue to register products containing boric acid or sodium borate with the appropriate precautionary labeling and use directions, providing the legal requirements for each registration are met.

7. While borax and boric acid differ chemically, there is essentially no difference in their toxicological effects or insecticidal activity, as the active part of the formulation is the borate ion.

8. Regarding the "conditional registration" of new pesticides mentioned in PR Notice 78-5, this statement refers to products containing new (not previously registered) active ingredients. Borax (and boric acid) have been used, in different formulations, for cockroach control for years, so for this proposed use it is not "new." An applicant seeking to register a product containing a new active ingredient would, at the very least, have to submit acute toxicological studies, since the Agency would not have any information on hand regarding possible hazards associated with exposure to this material. A conditional registration might be issued, but the applicant would have had to submit these studies, and would then probably be required to submit long term studies (possibly including a 2-year rat carcinogenicity study) within a certain period of time, or have the registration cancelled.

9. Regarding the labeling, although we would prefer the statement: "Apply in areas out of reach of children and pets. May be used in and around home and garage." we can accept the proposed statement: "Apply in areas out of reach of children and pets, in and around your home and garage."

10. We cannot allow a statement recommending reuse of the container (as indicated in the letter of May 7, 1979). The legal constraints which the Agency is working under require that we show no favoritism to one pesticide over others in this respect.

Byron T Backus 9/10/79

Byron T. Backus
IRB/TSS