CASWELL FILE

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

SEP - 8 1989

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: GX-071 - 90-Day Dog Study Protocol; Questions Re: Bridging Toxicology Data

TO: Michael Mendelson
Product Manager (17)
Registration Division (H7505C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 8/31/89
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Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 8/31/89
Acting Section II Head, Toxicology Branch II
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and

Marcia van Gemert, Ph.D. Marcia van Gemert 9/5/89
Chief, Toxicology Branch/HFAS/HED (H7509C)

Registrant: Griffin Corporation
Chemical: N-ethyl perfluorooctane sulfonamid
Synonyms: GX-071; sulfluramid
Project: 9-1954
Caswell No.: 454E
Record No.: 249695
Identifying No.: 1812-327
Action Requested: Review protocol for subchronic dog study and respond to questions raised in the letters (attached).

Comment: The Registrant has submitted 3 letters (each dated July 27, 1989) regarding N-ethyl perfluroooctane sulfonamid and a draft protocol for a 90-day feeding study in dogs. These are discussed below.

A. The first letter is a follow-up to a meeting held June 14, 1989, in which advice was sought with regard to the choice of test material to be utilized in future toxicology studies. Initially, the production of GX-071 resulted in a highly linear isomer product, and this was used in the initial setting of specifications/testing of the compound. With commercial production, however, the production of a highly linear product is ineffecient and expensive, and the resultant branched isomer has become a disposal problem. The raw product consists of an approximate 70:30 ratio of linear to branched isomers of N-ethyl perfluorooctane sulfonamid. In the production of sulfluramid, various methods of impurity removal result in different linear to branched isomer ratios of N-perfluorooctane sulfonamid. The Registrant is testing alternative methods of impurity removal and expects to develop all future registration data with a test sample representative of the product resulting from the improved production process. A toxicity screen (acute orals and 14 day rat dietary) is being conducted on the alternative process samples.

The Registrant expects to submit a revised product chemistry package and bridging toxicology data and asks whether a toxicity screen that includes an acute oral LD_{50}, a 14-day rat dietary, and a 10-week rat pilot study (side by side with sulfluramid at current specifications) is an appropriate bridging program.

Additionally, because of its desirable characteristics for certain end-uses, the sodium salt of sulfluramid may be developed for registration, and the Registrant asks what bridging toxicology data would be required.

TB II response: It is not clear to this reviewer what is meant by "bridging" toxicology data. The Registrant's proposed toxicity screen of the resultant product from the revised production process (revised product), which includes an acute oral LD_{50} study, a 14-day rat dietary study, and a 10-week rat pilot study (exposure route not specified) as well as comparable studies on the sulfluramid at current specifications (current product), will provide a basis on which to determine whether the current product differs substantially from the revised product in its toxicological effects. Any additional toxicological testing that may be required (depending on future proposed use patterns) should be performed on the revised production process product. Before a final determination can be made with regard to this aspect, however, input from product chemistry, etc., will need to be considered, especially with regard to the identity of possible impurities. Currently, the only toxicology data available, in addition to the above-referenced dog study, are acute studies and mutagenicity data on the "current product", and the only approved use is in ant and roach bait traps.

With regard to the sodium salt of sulfluramid, toxicology data on the technical product are generally adequate, provided the production process is similar to that of the technical compound.

B. In the second letter, efforts to address the results of a dog study performed at the University of Georgia on sulfluramid are described. The Registrant is preparing to conduct subchronic feeding studies in dogs and rats and a draft protocol for the dog study was submitted (protocol re-submitted on 8/22/89; previous copy was apparently a preliminary one). As discussed in the letter, they wish to use dogs that are older than normally used in a subchronic study. The arguments put forth in support of the use of older dogs include

a) the test material is more toxic in mature male dogs (from previous UG study);
b) sperm counts can be evaluated regularly from mature dogs;
c) lack of sperm in maturing dogs can be assessed only by histological evaluation at study termination.

TB II response: With regard to the draft protocol, in general it is adequate (except as noted below). However, there are no dose levels provided nor any information on how the dose levels will be chosen.

While the use of mature dogs to address the apparent decrease in spermatogenesis is appropriate, the objective of the 90-day study (as stated) is to "evaluate the possible toxic effect of the test material when administered to dogs for 90 days." Therefore, the use of mature dogs only would not satisfy the study requirement. It would be appropriate, however, to include additional groups of mature males as "satellite" groups for the specific purpose of addressing the issue of decreased spermatogenesis. The full range of parameters usually monitored in a 90-day study need not be for these satellite groups.

Although the submitted protocol will need to be modified, in light of the foregoing discussion, the following comments are offered on the protocol as written.

1) With regard to the protocol (not identified as such), on page 4 under D.1., the statement: "Evaluations at the end of the recovery period will be those showing effect at the end of the treatment period only." is unclear.
2) On page 5 under D.3., the treatment regimen needs to be modified. Since there will be a recovery group, which will not receive test material "until all animals are sacrificed", the first statement in the paragraph is inaccurate.
3) On page 6 under VIII. E., the first sentence is incomplete. It would appear that it should read: ..... beginning two weeks prior to study initiation.

C. In the third letter, the Registrant provides a record of the agreements reached at a June 27, 1989 meeting between Griffin and EPA personnel regarding the UDS assay. The Registrant has agreed to provide supplemental data on dose levels of GX-071 between 1.0 and 2.5 ug/ml from a repeat of the UDS assay. These data are to be submitted in September, 1989, according to the letter.

No TB II comment is required.