2,4-D/TOX

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

TO: Lois Rossi
2,4-D Project Manager
SPRD/OPTS

THRU: R. Bruce Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

7/23/82

Orville E. Paynter, Ph.D.
Toxicology Branch/HED (TS-769)

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SUBJECT: 2,4-D Data Call-in, Bioequivalency

Background:

In response to the August 29, 1980, 2,4-D Order and Notice large-production registrants of 2,4-D products formed an industry Task Force in an effort to pool resources and reduce duplication of costly data that was required. Several of the registrants however took exception to the notice which stated that individual studies such as teratology were required for the acid, salts and individual esters. Position Paper No. 1 was the Task Forces effort in reasoning why a bioequivalency existed for these products. The final opinion being that the results from a study using technical 2,4-D acid would adequately represent the teratogenicity potential of all other salts and esters of 2,4-D.

A letter from John Conner, Esq. to Mr. E. Johnson dated April 28, 1982 formally requested that the Agency respond to Position Paper No. 1. At the same time "Protocols for Toxicity Testing" were submitted for review and comment on June 1, 1982 to representatives of the Task Force. No formal written statement was presented to the Task Force at the meeting due to time constraints. Following are the formal comments on the question of bioequivalenecy.

Position:

1. The TOX Branch does not believe that essential bioequivalency has been shown for 2,4-D acid and 2,4-D esters.

2. Data submitted or referenced by the industry task force however does at least suggest that the salts may hydrolze in the stomach so that only the 2,4-D acid is found in the blood stream.

3. In order to accept the claim of a bioequivalency for esters or salts in general the TOX Branch considers it necessary to conduct in vivo hydrolysis assays on those products in question.

Rationale:

1. The industry task force suggested that the teratology study by Unger et al. 1981 provided evidence that the acid and two esters, PGBE and isooctyl were equivalent by comparing the NOEL for toxicity. Since toxicity was not reported excepting as a slight increase in rib buds following exposure to either ester, an adequate end point for comparison in this study is absent.

2. More refined general methods for quantitation of individual chemicals are available, and using the sensitive methodology of gas chromatography the extra step of acid hydrolysis and quantitation by differences is eliminated. The butyl ester of 2,4-D was found in the plasma and red blood cells of pigs tested by Erne, 1966. True, the esters may be rapidly hydrolzed in the body but the question of whether the esters would reach the fetus prior to hydrolysis has not been verified.

Absorption profiles for an amine, salt of 2,4-D have been reported in graph form by Erne, 1966 in a second paper. This data suggests that differences may exist between rodents and pigs, calves or chickens. Differences in plasma peak levels and time to maximum concentration also are evident for a single oral 100 mg/kg dose of 2,4-D butyl ester when comparing with those same species values for 2,4-D amine.

Henry Spencer, Ph.D. Henry 7/21/82.
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