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SECTION HEAD

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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Cacodylic Acid: Registrant's Response to Agency's Review of Toxicology Data

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Tox. Branch II, Review Section IV
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TO: Virginia Dietrich, Product Manager (51);
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THRU: Jess Rowland, M.S., Acting Section Head Jess Rowland 9/10/93
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and

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Task Identification: Submission: S442517 DP Barcode: D192215
P.C. Code: 012501 Caswell No.: 133

ACTION REQUESTED: Review registrants response to upgrade Combined Chronic Toxicity/Carcinogenicity Study - Rat that was classified as Supplementary.

SUMMARY:

The Combined Chronic Toxicity/Carcinogenicity study with Cacodylic Acid in rats [MRID No. 418621-01] was Core Classified as Supplementary [Memo: S. Malish to Barbara Brisco 3/30/92; HED document No. 009391]. It was noted that the study may be upgraded by providing an explanation or justification for the doses employed in the test study.

The registrant submitted the results of a 90 - day oral toxicity study [MRID 427677-01] which was used to select the dose levels for the Combined Chronic Toxicity/Carcinogenicity study with Cacodylic Acid in rats.

Since the high dose of 100 ppm used in the Combined Chronic Toxicity/Carcinogenicity Study was within the range suggested by the subchronic oral toxicity study, the combined chronic toxicity/ Carcinogenicity Study, [MRID 418621-01] previously classified as Supplementary is upgraded to Minimum.

I. BACKGROUND:

The registrant submitted a Subchronic Oral Toxicity: 90 Day Study/Rat [MRID No. 427677-01] and an accompanying letter [MRID No. 427677-00] to upgrade previous study submission Combined Chronic Toxicity/Oncogenicity Study, [MRID 418621-01].

AUTHOR:	S. Crown, G. Kenan; et. al.
STUDY NUMBER:	PAL/009/CAC
REPORT ISSUED:	May 1987
REGULATORY COMPLIANCE:	A statement of compliance with Good Laboratory Practice Standards and a Statement of no data confidentiality claims was signed and dated.

II. REVIEW of SUBMITTED DATA:

The Combined Chronic Toxicity/Oncogenicity Study (83-5), [MRID 418621-01] was Core Classified as supplementary because a MTD was not specifically established, the decrease in the rate of weight gains were $\leq$10% in both males and females.

A Data Evaluation Report for the 90-Day study is attached. Results show that a NOEL of 5 ppm and a LOEL of 50 ppm based on mortality, decreased body weight gain, alterations in hematology, changes in absolute and relative organ weights and histopathological lesions. The target organs were the thyroid, kidney, aorta, bone marrow, heart, testes and uterus.

III. DISCUSSION:

A 13 week study usually defines the toxicity profile (with the exception of carcinogenicity and other life-shortening toxicities) and can be used to establish doses to be employed in the carcinogenicity study.

It is the Agency's position that a dose be used in the carcinogenicity study that decreases the rate of weight gain by

≥10%, the so called Maximum Tolerated Dose (MTD), unless there is justification that this dose cannot be used because of the potential for a toxic effects or pathological alteration that would decrease survival on prolonged exposure. Thus the high dose should be adequate to assess the carcinogenic potential of the test material.

The data derived from the subchronic oral toxicity study in rats presented clinical pathology changes, organ weight and pathological alterations at 50 ppm; at 500 ppm mortality, body weight changes, clinical pathology changes, organ weight and pathological alterations occurred. These facts suggested that a dose >50 but substantially less than 500 ppm should be chosen for the high dose in the carcinogenicity study.

A dose of 100 ppm was used as the high dose for the Combined Chronic Toxicity/Carcinogenicity Study which was in the range suggested by the subchronic oral toxicity study.

IV. CONCLUSIONS:

The data submitted by the registrant is satisfactory with regard to the doses complying with the Combined Chronic Toxicity/ Carcinogenicity Study (83-5), [MRID 418621-01]. Consequently this dose classified as Supplementary is upgraded to Minimum.

V. CORE CLASSIFICATION:

The Combined Chronic Toxicity/Carcinogenicity Study (83-5), [MRID 418621-01] is upgraded to Minimum satisfying the data requirements 83-5 and is acceptable for regulatory purposes.