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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

TO: G. Werdig
Registration Division (TS 767C)

THRU: Judith Hauswirth, Ph. D., Acting Head
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS 769) Judith W. Hauswirth 2/6/87

FROM: Roger Gardner, Toxicologist
Review Section 6
Toxicology Branch Roger Gardner 2-6-87
Hazard Evaluation Division (TS 769) for WHS 2/24/87

SUBJECT: Ammended Protocol for a Mouse Oncogenicity Study on MSMA. Tox. Chem. No. 582; Tox. Project No. 7-0328

Action Requested

Recommendations on a requested extension of the time for completion of a mouse oncogenicity study with monosodium methanearsonate (MSMA).

Recommendations and Conclusions

Based on the circumstances of violent behavior and excess mortality among male mice in the MSMA oncogenicity study, the requested extension of a Data Call-In (DCI) deadline is justified (see "Discussion" below).

Discussion

In a letter dated December 31, 1986, the Registrant (Fermenta Plant Protection Company) requested a meeting with the Agency to discuss the following:

1. The Registrant's interpretation of results leading to termination of the subject long-term study.

2. Results of necropsy, histological, and clinical observations of the surviving animals in the terminated study including data documentation and record keeping.

3. Protocol amendments and a request for extension of a DCI deadline so another oncogenicity study in mice can be conducted.

4. A new protocol

Attached to the letter were copies of the original protocol, amendments to that protocol, and a status report on the original study (dated December 24, 1986).

According to the amendments, male mice had to be caged individually after four weeks of the study because of violent behavior when they were gang caged (4/cage). Additional animals were placed in the study during the first eight weeks as needed, and the two highest doses were both lowered from 2500 and 4000 ppm to 1800 ppm because of excessive mortality. The mortality rate continued to be high in mice given the 1800 ppm diet, and the study was terminated after 38 weeks. The status report included with the Registrant's letter indicated the following mortality:

Group number	Dose level (ppm)	Males		Females	
		Deaths	Survivors	Deaths	Survivors
1	0	7	52	1	55
2	300	0	56	0	56
3	1100	37	27	0	56
4	2500/1800	26	32	7	49
5	4000/1800	22	34	13	43

The mortality results indicate that doses were too high for males, and survival in two of the three highest dosed groups was below 50% before a duration approximating the lifespan of mice could be reached. Therefore, the decision to terminate the study was appropriate.

If formally submitted to the Agency, the additional data included in the December status report would be useful to support a rationale for dose selection or characterization of a Maximum Tolerated Dose.

2