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INDUSTRIAL HEALTH FOUNDATION, INC.
A NONPROFIT ORGANIZATION FOR THE ADVANCEMENT OF HEALTHFUL WORKING CONDITIONS
ESTABLISHED 1935
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8EHQ-0990-1063 INITIAL

8-pages

August 29, 1990

88-900000235
EPA-OTS
0010341118

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CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Document Processing Center (TS-790)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Reference: Methylethylketoxime(MEKO)
Submission of information
from Reproduction Study
in Rats

Attention: Section 8(e) Coordinator

At the request of the companies supporting studies on methylethylketoxime, under IHF auspices, we have been asked to submit findings obtained in the course of performance of a two-generation study on MEKO which is being run as part of the Section 4 Test Rule for MEKO. The companies requesting this submission are as follows: Allied-Signal Inc., Huls America, Inc., AKZO Chemicals, Inc., Aceto Corporation, Mooney Chemical Inc., Troy Chemical Company and Dussek Campbell Ltd.

Attached is a copy of a letter from the performing laboratory which notes mortality in males and females at the high dose level of 200 mg/kg. This mortality was as of the end of eight weeks of dosing; animals had not yet been mated. A prior study performed by Allied-Signal Corporation in 1977 showed no mortality after thirteen weeks at a dose level of 225 mg/kg. Sprague-Dawley rats were used for both studies and the material was administered by gavage in both cases. The only difference between the studies to this point is that the early study used methyl cellulose solution as the vehicle whereas the current study uses water solutions.

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The data from the current study is unexpected and, at this point, unexplainable. However, it suggests a greater degree of sub-acute toxicity from MEKO than previously inferred. This constitutes our reason for submission of the findings at this time.

A copy of the full report will be submitted to EPA when finalized by the testing laboratory in fulfillment of the requirements of the Section 4 Test Rule for MEKO.

Sincerely,

William E. Rinehart

William E. Rinehart, Sc.D.
President
Agent for Committee on
Toxicology of MEKO

WER/ac

Enclosure

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RESEARCH TRIANGLE INSTITUTE

RTI

Chemistry and Life Sciences
Center for Life Sciences and Toxicology

August 20, 1990

AUG 22 1990

90 SEP -7 PM 2:35

Dr. William E. Rinehart, President
Industrial Health Foundation, Inc.
34 Penn Circle West
Pittsburgh, PA 15206

RE: RTI Project No. 60C-4692

Dear Dr. Rinehart:

As you know, we are currently performing a two-generation reproductive toxicity study of methylethyl ketoxime (MEKO) administered by gavage to CD® (Sprague-Dawley) rats. We have just completed the eighth week of the F0 pre-breed exposure period, dosing the animals five days/week at 0, 50, 100 or 200 mg/kg/day at a dosing volume of 2.0 ml/kg. There are 30 animals/sex/dose.

We are observing unanticipated mortality at 200 mg/kg/day: as of Friday, August 17, 1990, 11 of 30 females have died and four (4) of 30 males (the death of one of the males was due to a dosing error). The animal number, study day of death, and clinical signs preceding demise are presented in Table 1. Rooting in bedding ("snowplowing"), evidence of chromodacryorrhea, respiratory difficulty and possible CNS involvement (tremors, stupor, convulsions) were observed in these animals. We necropsied all animals which died and noted only enlarged and darkened spleens in the treatment-related deaths.

My group and our Quality Assurance Group have rechecked the data on dosing solution formulation, analysis and administration; there are no errors. The analysis on the test chemical performed at RTI indicates >99% purity as mandated by the MEKO Test Rule. There was no pattern to the day of the week the deaths occurred; most of the animals were found dead in the morning prior to dosing so they died between the pm dead check the day before and the am time of dosing.

Please let me know at your earliest convenience if you need any further information or anticipate any changes to the study design. We are scheduled to begin the three-week mating period on August 28, 1990 (animals paired; first gd 0 August 29).

Post Office Box 12194 Research Triangle Park, North Carolina 27709 Telephone: 919 541-6000

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Thank you for your continued cooperation.

Sincerely,

Rochelle W. Tyl

Rochelle W. Tyl, Ph.D., DABT
Study Director/Senior Program
Director, Developmental and
Reproductive Toxicology

RWT:ng

Enclosures

cc: Dr. F. J. de Serres, Director, CLST
Dr. A. R. Jeffcoat
Ms. C. B. Myers
Ms. M. C. Marr
Ms. D. R. Brine
Ms. S. M. Taulbee, QA
Ms. C. S. Parker, Contracts

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Clinical Signs for MEKO Females that had Died or were Sacrificed
by August 17, 1990

Day	Clinical Observation	Animal No.
2	Audible Respiration	184
	Involuntary Facial Tremors: Postdosing	6
	Rooting in Bedding	106
3	Light Colored Feces	80
	Rooting in Bedding	16, 36, 42, 80, 106 and 130
6	Weaving	6
	Rooting in Bedding	42, 116, 130 and 166
	Tremors	36
7	Rooting in Bedding	6, 16 and 42
8	Rooting in Bedding	16, 42, 80, 106, 130, 166 and 206
9	Rooting in Bedding	16, 130, 166
	Weaving	184
10	Rooting in Bedding	16, 42, 80, 130, 166 and 184
	Tremors	36
	Audible Respiration	36
13	Weaving	6
	Rooting in Bedding	80, 130 and 166
14	Rooting in Bedding	80, 106, 130, 166 and 184
15	Rooting in Bedding	80 and 166
16	Rooting in Bedding	16, 36, 130, 166, 184 and 206
17	Rooting in Bedding	16, 36 and 80
20	Rooting in Bedding	16, 42 and 80
21	Rooting in Bedding	16, 80, 130, 166, 184 and 2[illegible]
	Weight Loss of 7.40 g.	6
22	Rust Colored Fur on Face	6
	Red Nasal Discharge	6
	Rooting in Bedding	6, 16, 80, 166 and 184
	Gasping, Audible Labored Respiration	6
	Ataxia	6
	Found Dead in the Afternoon	6
23	Rooting in Bedding	16, 32, 36, 80, 166 and 206
24	Rooting in Bedding	16, 32, 36, 80, 130, 166 and 184
27	Rooting in Bedding	36
28	Rooting in Bedding	16, 36, 42, 80 and 166

(continued)

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Clinical Signs for MEKO Females that had Died or were Sacrificed by August 17,1990 (continued)

Day	Clinical Observation	Animal No.
29	Rooting in Bedding	16, 36, 130 and 166
	Red Nasal Discharge	106
30	Rooting in Bedding	16, 36, 42, 130 and 166
31	Rooting in Bedding	16, 32, 36, 130 and 166
	Alopecia: Right Side	80
32	Alopecia: Right Side	80
34	Rooting in Bedding	16, 42 and 166
	Alopecia: Right Side	80
35	Rooting in Bedding	16, 36, 42 and 166
	Red Nasal Discharge	106
	Alopecia: Right Side	80
36	Rooting in Bedding	16, 36, 42 and 166
	Alopecia: Right Side	80
	Audible Respiration	130
37	Rooting in Bedding	16
	Alopecia: Right Side	80
38	Rooting in Bedding	16
	Red Nasal Discharge	206
	Alopecia: Right Side	80
39	Alopecia: Right Side	80
40	Alopecia: Right Side	80
41	**Found Dead in the Morning**	**16**
	Alopecia: Right Side	80
42	Alopecia: Right Side	80
43	Rooting in Bedding	32, 36, 42, 80, 106, 130, 166 and 184
	Alopecia: Right Side	80
44	Rooting in Bedding	36
	Found Dead in the Morning	**106**
45	Dehydrated	36 and 206
	Difficulty Breathing: Postdosing	36
	Labored Respiration, Gasping	36 and 206
	Red Nasal Discharge	36 and 206
	Rooting in Bedding	36, 80, 130, 166 and 184
	Rust Colored Fur on Face	36 and 206
	Urine Very Yellow	36

(continued)

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Clinical Signs for MEKO Females that had Died or were Sacrificed
by August 17,1990 (concluded)

Day	Clinical Observation	Animal No.
45	Sacrificed in extremis	206
48	Found Dead in the Morning	36
	Rooting in Bedding	32, 42, 130, 166 and 184
49	Rooting in Bedding	32, 42, 80, 130, 166 and 184
	Weight Loss of 5.47 g.	80
50	Rooting in Bedding	32, 42, 80, 130, 166 and 184
51	Found Dead in the Morning	184
53	Audible Respiration	42
54	Irregular Respiration	42
55	Found Dead in the Morning	42
	Rooting in Bedding	80, 130 and 166
56	Rooting in Bedding	32, 80 and 166
	Red Nasal Discharge	32
	Labored Respiration	32
	Weight Loss of 11.34 g.	32
	Weight Loss of 12.91 g.	130
	Sacrificed in extremis	32
57	Rooting in Bedding	80 and 166
	Found Dead in the Morning	130
58	Rooting in the Bedding	166
	Ataxia	80
	Red Nasal Discharge	80
	Convulsed: Postdosing	80
	Found Dead in the Afternoon	80 and 166

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Clinical Signs for MEKO Males that had Died or were Sacrificed
by August 17,1990

Day	Clinical Observation	Animal No.
2	Rooting in Bedding	53
	Salivating: Postdosing	91
	Tremors	139
3	Rooting in Bedding	119
	Salivating: Postdosing	91
6	Rooting in Bedding	53 and 119
	Salivating: Postdosing	91
7	Stupor	53
10	Rooting in Bedding	53 and 119
13	Rooting in Bedding	53 and 119
	Tremors	53
14	Rooting in Bedding	53 and 139
15	Rooting in Bedding	91 and 119
16	Rooting in Bedding	53, 91 and 139
17	Rooting in Bedding	53, 91, 119 and 139
20	Rooting in Bedding	53, 91, and 139
22	Rooting in Bedding	53, 91, 119 and 139
23	Rooting in Bedding	53 and 139
24	Rooting in Bedding	53, 91, and 139
27	Rooting in Bedding	119
29	Rooting in Bedding	53
	Sacrificed in extremis	119 (dosing error)
31	Red Nasal Discharge	91
34	Rooting in Bedding	53
35	Rooting in Bedding	53 and 139
42	Found Dead in the Morning	139
43	Rooting in Bedding	53 and 91
45	Rooting in Bedding	53 and 91
48	Rooting in Bedding	53
49	Found Dead in the Morning	53
50	Rooting in Bedding	91
53	Found Dead in the Morning	91