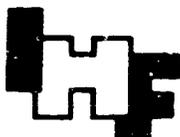


Contains No CBI

8E Supplement



8EHQ-1293-1063

INDUSTRIAL HEALTH FOUNDATION, INC.

A NONPROFIT ORGANIZATION FOR THE ADVANCEMENT OF HEALTHFUL WORKING CONDITIONS

ESTABLISHED 1935

34 PENN CIRCLE WEST • PITTSBURGH, PA 15206 • (412) 363-6600

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December 1, 1993

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Document Control Officer
Chemical Information Division
Office of Toxic Substances
Room E-108
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

EPA-OTS



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SPD 8-19-93

REC'D
OFFICE OF POLLUTION
PREVENTION AND TOXICS
93 DEC - 6 AM 11:20

RE: Notice of Substantial Risk Under TSCA 8(e) for Methyleneketoxime (MEKO) when Administered by Inhalation to Rats and Mice in an Oncogenicity Study. Addendum to Notices Submitted on May 28, 1992, February 5, 1993 and February 12, 1993 (by Akzo Chemical) regarding findings in rats.

EPA Docket No. 8EHQ-0990-1063

Attention: Section 8(e) Coordinator

Dear Sir:

The Industrial Health Foundation, Inc. (IHF) submits this notification as agent for and in behalf of the sponsors of the subject study (AlliedSignal, Inc.; Akzo Chemicals, Inc.; Huls America, Inc.; Aceto Corporation; Dussek Campbell, Ltd.; Troy Chemical Company; and Mooney Chemicals, Inc.) in accordance with Section 8(e) of the Toxic Substances Control Act and EPA's statement of Interpretation and Enforcement Policy, 43 Fed. Reg. 1110 (March 16, 1978). The described testing herein was initiated in response to the EPA Final Test Rule for Methyleneketoxime (MEKO) under section 4 of TSCA (Fed. Reg. 54(176), 37799, September 13, 1989). This study was performed to evaluate the potential for toxic and oncogenic effects of MEKO when administered by inhalation to rats for 26 months and mice for 18 months.

The submission of May 28, 1992 from IHF indicated an increased incidence of visually observed cataracts in rats at 18 months after initiation of exposure. The submissions of February 5, 1993 and February 12, 1993 from Akzo Chemicals described a number of findings observed at terminal necropsy at approximately 26 months after initiation of exposure which included the presence of liver nodules. This submission is to provide notice of significant findings as determined from the unaudited draft pathology report on rats.

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There is a dose-related increase in olfactory epithelial degeneration, especially in nasal sections 2-4, as was seen in mice. Unfortunately, this was not noted in the high dose group by the laboratory pathologist for the 12 and 18 month interim sacrifices and, therefore, the nasal tissues were not designated as a target organ requiring evaluation of the low and middle exposure levels for the scheduled sacrifices. This evaluation has now been authorized and is in progress. It seems clear, however, that the effect was not evident until sometime after 3 months of exposure.

There is also a dose-related increase in the incidence of liver adenomas in both sexes and an increase in liver carcinomas in male rats. This effect did not seem to develop until after 18 months of exposure.

A slight but clear increase in bilateral cataracts has been confirmed histopathologically for the high exposure level in both sexes. You will recall that an increase was noted in visible cataracts at 18 months and was reported as an 8(e) finding. It should also be noted that histopathologic confirmation of cataracts is difficult and therefore possibly less reliant than the information gained from an in-life ophthalmoscopic examination.

You will note a few discrepancies (denominators) between the total incidence rates of the various findings which I generated by simple addition of data from the tables of interim and terminal sacrifices plus that for the non-scheduled deaths and the incidences noted in the laboratory's tabulation of all deaths. I suspect this relates to the several replacement animals during the first month of study and that these may not have been uniformly included with the unscheduled deaths. The laboratory will check this on final audit.

Enclosed for your review are copies of the summaries of the significant findings as they occurred over time. These tables were generated by us from the unaudited draft pathology report.

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The complete audited final report on this study is expected to be available in March, 1994 and you will be provided with a copy of the final report at that time.

If there are any questions regarding this submission, please contact me at 412/363-6600.

Sincerely,


William E. Rinehart, Sc.D.
President
(Agent for the MEKC Testing Group)

WER:la

Enclosures

**2-Year Inhalation Study of MEKC in Rats
Incidence of Significant Pathologic Findings**

Olfactory Epithelial Degeneration, Section 1

| | <u>Males ppm</u> | | | | <u>Females ppm</u> | | | |
|-------------------------|------------------|------|------|------|--------------------|------|------|------|
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | | | 0/10 | 0/10 | | | 0/10 |
| 12 month Interim | 0/10 | | | 0/10 | 0/10 | | | 0/9 |
| 18 month Interim | 0/10 | | | 0/9 | 0/10 | | | 0/10 |
| Terminal sacrifice | 0/17 | | | 0/22 | 0/27 | | | 0/39 |
| Unscheduled deaths | 0/32 | 0/31 | 0/36 | 0/27 | 0/18 | 0/20 | 0/20 | 0/12 |
| Total (by addition) | 0/79 | 0/31 | 0/36 | 0/78 | 0/75 | 0/20 | 0/20 | 0/80 |
| Total (from tabulation) | 0/80 | 0/32 | 0/36 | 0/78 | 0/75 | 0/20 | 0/21 | 0/80 |

2-Year Inhalation Study of MEK₀ in Rats
 Incidence of Significant Pathologic Findings

Olfactory Epithelial Degeneration, Section 2

| | <u>Males ppm</u> | | | | <u>Females ppm</u> | | | |
|-------------------------|------------------|-------|-------|-------|--------------------|------|-------|-------|
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | | | 0/10 | 0/10 | | | 0/8 |
| 10 month Interim | 0/10 | | | 4/10 | 0/10 | | | 4/9 |
| 18 month Interim | 0/10 | | | 6/9 | 0/10 | | | 9/10 |
| Terminal sacrifice | 0/17 | | | 19/20 | 0/30 | | | 33/38 |
| Unscheduled deaths | 1/33 | 17/32 | 24/36 | 22/26 | 0/18 | 8/20 | 16/19 | 10/12 |
| Total (by addition) | 1/80 | 17/32 | 24/36 | 51/75 | 0/78 | 8/20 | 16/19 | 56/77 |
| Total (from tabulation) | 1/81 | 17/33 | 24/36 | 51/75 | 0/78 | 8/20 | 16/20 | 56/77 |

2-Year Inhalation Study of MEKO in Rats
Incidence of Significant Pathologic Findings

Olfactory Epithelial Degeneration, Section 3

| | <u>Males ppm</u> | | | | <u>Females ppm</u> | | | |
|-------------------------|------------------|------|-------|-------|--------------------|------|-------|-------|
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | | | 0/9 | 0/10 | | | 0/5 |
| 12 month Interim | 0/10 | | | 4/8 | 0/6 | | | 2/8 |
| 18 month Interim | 0/8 | | | 5/6 | 0/9 | | | 4/9 |
| Terminal sacrifice | 0/15 | | | 21/21 | 0/23 | | | 28/29 |
| Unscheduled deaths | 0/32 | 7/29 | 20/29 | 18/22 | 0/14 | 0/15 | 10/13 | 5/9 |
| Total (by addition) | 0/75 | 7/29 | 20/29 | 48/66 | 0/62 | 0/15 | 10/13 | 39/60 |
| Total (from tabulation) | 0/76 | 7/30 | 20/29 | 48/66 | 0/62 | 0/15 | 10/14 | 39/60 |

2-Year Inhalation Study of MEKO in Rats
 Incidence of Significant Pathologic Findings

Olfactory Epithelial Degeneration, Section 4

| | <u>Males ppm</u> | | | | <u>Females ppm</u> | | | |
|-------------------------|------------------|------|-------|-------|--------------------|------|-------|-------|
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | | | 0/9 | 0/7 | | | 0/10 |
| 12 month Interim | 0/6 | | | 8/8 | 0/10 | | | 4/8 |
| 18 month Interim | 0/10 | | | 8/9 | 0/9 | | | 0/6 |
| Terminal sacrifice | 1/17 | | | 18/19 | 0/28 | | | 27/31 |
| Unscheduled deaths | 1/31 | 2/26 | 16/32 | 19/25 | 0/17 | 0/17 | 13/18 | 7/12 |
| Total (by addition) | 2/74 | 2/26 | 16/32 | 53/71 | 0/71 | 0/17 | 13/18 | 38/67 |
| Total (from tabulation) | 2/74 | 2/27 | 16/32 | 53/71 | 0/71 | 0/17 | 13/19 | 38/67 |

**2-Year Inhalation Study of MEKO in Rats
Incidence of Significant Pathologic Findings**

Liver Adenomas

| | <u>Males ppm</u> | | | | <u>Females ppm</u> | | | |
|-------------------------|------------------|------|------|-------|--------------------|------|------|------|
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 |
| 12 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/9 |
| 18 month Interim | 0/10 | 0/9 | 0/9 | 0/9 | 0/10 | 0/10 | 0/10 | 0/10 |
| Terminal sacrifice | 0/17 | 1/19 | 3/14 | 8/22 | 0/30 | 0/29 | 2/30 | 4/39 |
| Unscheduled deaths | 0/33 | 1/32 | 2/37 | 10/29 | 0/20 | 0/21 | 0/20 | 0/12 |
| Total (by addition) | 0/80 | 2/80 | 5/80 | 18/80 | 0/80 | 0/80 | 2/80 | 4/80 |
| Total (from tabulation) | 0/81 | 2/81 | 5/80 | 18/80 | 0/80 | 0/80 | 2/81 | 4/80 |

2-Year Inhalation Study of MEKO in Rats
Incidence of Significant Pathologic Findings

Liver Carcinomas

| | <u>Males ppm</u> | | | | <u>Females ppm</u> | | | |
|-------------------------|------------------|------|------|-------|--------------------|------|------|------|
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 |
| 12 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/9 |
| 18 month Interim | 0/10 | 0/9 | 0/9 | 0/9 | 0/10 | 0/10 | 0/10 | 0/10 |
| Terminal sacrifice | 0/17 | 0/19 | 1/14 | 8/22 | 0/30 | 0/29 | 0/30 | 0/39 |
| Unscheduled deaths | 0/33 | 0/32 | 0/37 | 4/29 | 0/20 | 0/21 | 0/20 | 0/12 |
| Total (by addition) | 0/80 | 0/80 | 1/80 | 12/80 | 0/80 | 0/80 | 0/80 | 0/80 |
| Total (from tabulation) | 0/81 | 0/81 | 1/80 | 12/80 | 0/80 | 0/80 | 0/81 | 0/80 |

2-Year Inhalation Study of MEKO in Rats
Incidence of Significant Pathologic Findings

| | Liver Adenomas and Carcinomas, Combined | | | | | | | |
|-------------------------|---|------|------|-------|-------------|------|------|------|
| | Males ppm | | | | Females ppm | | | |
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 |
| 12 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/9 |
| 18 month Interim | 0/10 | 0/9 | 0/9 | 0/9 | 0/10 | 0/10 | 0/10 | 0/10 |
| Terminal sacrifice | 0/17 | 1/19 | 4/14 | 16/22 | 0/30 | 0/29 | 2/30 | 4/39 |
| Unscheduled deaths | 0/33 | 1/32 | 2/37 | 14/29 | 0/20 | 0/21 | 0/20 | 0/12 |
| Total (by addition) | 0/80 | 2/80 | 6/80 | 30/80 | 0/80 | 0/81 | 2/80 | 4/80 |
| Total (from tabulation) | 0/81 | 2/81 | 6/80 | 30/80 | 0/80 | 0/80 | 2/81 | 4/80 |

2-Year Inhalation Study of MEKO in Rats
 Incidence of Significant Pathologic Findings

Bilateral Cataracts

| | <u>Males ppm</u> | | | | <u>Females ppm</u> | | | |
|-------------------------|------------------|-------|-------|-------|--------------------|-------|-------|-------|
| | 0 | 15 | 75 | 375 | 0 | 15 | 75 | 375 |
| 3 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 |
| 12 month Interim | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 |
| 18 month Interim | 0/10 | 0/9 | 0/9 | 0/9 | 1/10 | 0/10 | 1/10 | 1/10 |
| Terminal sacrifice | 12/17 | 14/18 | 5/9 | 19/22 | 27/30 | 17/24 | 23/30 | 39/39 |
| Unscheduled deaths | 16/33 | 14/32 | 9/37 | 20/23 | 10/20 | 9/20 | 7/20 | 9/12 |
| Total (by addition) | 28/80 | 28/79 | 14/75 | 39/80 | 38/80 | 26/74 | 31/80 | 49/80 |
| Total (from tabulation) | 28/81 | 28/80 | 14/75 | 39/80 | 38/80 | 26/74 | 31/81 | 49/80 |

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