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Chemicals Division

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January 22, 1992

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

8EHQ-0192-1063 SUPP

Re: Notice of Substantial Risk Under TSCA 8(e) for Methylethylketoxime (MEKO) when Administered by Gavage to Rats in a 2-Generation Reproduction Toxicity Study

EPA Docket No.: 8EHQ-0990-1063

PDCN: 8890000235

Dear Sir:

Akzo Chemicals Inc. (ACI) submits this notification 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 Methylethylketoxime (MEKO) under section 4 of TSCA [Fed. Register 54(176), 37799, September 13, 1990]. This study was performed to evaluate the reproductive toxicity potential of MEKO when administered to rats by oral gavage over two generations.

Accordingly, ACI is advising the EPA of preliminary and unaudited draft results of MEKO (CAS No. 96-29-7) in an oral two-generation reproduction study in Sprague-Dawley rats conducted at Research Triangle Institute (Study No. 60C-4692). The in-life phase of this study is complete and the draft final report is currently being audited. The final report will be submitted to the Agency in March 1992.

Experimental Design

Male and female CD (Sprague-Dawley) weanling rats (the F0 generation) were administered Methylethylketoxime in deionized/distilled water by gavage at 0, 10, 100 and 200.0 mg/kg/day, 30 animals/sex/dose, for ten (10) weeks. Vaginal cytology evaluation of F0 females was performed during the last three (3) weeks of the prebreed exposure period. Body weights and food consumption were recorded weekly, clinical observations at least once daily. Animals were then randomly mated within groups for three-week mating period to produce the F1 generation, with dosing continued.

EPA-OTS

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F0 males were necropsied after the mating period, with hematologic evaluation on 10/dose and histologic evaluation of reproductive and target tissues for high dose and control males (testes, livers and spleens were evaluated at all doses). F1 litters were culled to eight (8) pups on postnatal day (pnd) 4 and weaned on pnd 21. At weaning, 10 weanlings/sex/dose were evaluated hematologically and were necropsied; all non-selected F1 female weanlings had histological evaluation of inguinal mammary glands. F0 females received a two-week post-wean vaginal cytology evaluation and were then necropsied with hematologic evaluation of 10/sex/dose and histopathology of reproductive and target organs for high dose and control animals mammary glands, livers and spleens were evaluated at all doses. Selected F1 weanling, 30/sex/dose, were administered MEKO by gavage for an 11-week prebreed exposure period (with a three week prebreed vaginal cytology evaluation of F1 females) and then mated for three-week mating period as described above. Because of poor reproductive performance of F1 animals in producing F2 litters (not treatment- or dose-related), F1 animals unsuccessful in the first mating to produce F2a litters were rebred to produce F2b litters. At weaning of F2a litters, 10 weanlings/sex/dose were evaluated for hematology and necropsied; all non-selected F2a female weanlings were evaluated for inguinal mammary gland histopathology. After a two-week postwean vaginal cytology evaluation in F1 females, and prebreed vaginal cytology evaluation in initially unsucessful females with dosing continued, initially unsuccessful F1 adults were rebred for three weeks and F2b litters were raised. F1 males were necropsied after the mating, with hematology and histopathology as described above. At weaning of F2b litters, all F2b weanling females were evaluated for inguinal mammary gland histopathology, rebred F1 females received a two-week postwean vaginal cytology evaluation and all F1 females were then necropsied with hematology and histopathology as described above.

Adult Toxicity

Adult toxicity was observed in both generations and in both sexes at all doses of MEKO with clear dose-related incidences and severity of the findings. At 200 mg/kg/day, adult mortality occurred with consistent reductions in body weights and food consumption during the F0 and F1 prebreed exposure periods; clinical signs of toxicity were also consistently observed. Consistent evidence of treatment-related anemia was observed at 200 mg/kg/day with concomitant histologic evidence of extramedullary hematopoiesis and hemosiderosis in adult livers and spleens; spleen weights were increased at this dose as well. At 100 mg/kg/day, body weights and food consumption were occasionally reduced, and clinical signs of toxicity were observed. Anemia was also observed at this dose with associated liver and spleen histopathology and increased spleen weights; no treatment-related mortality occurred at this dose. At 10 mg/kg/day, only the histologic evidence of extramedullary hematopoiesis and hemosiderosis was observed in spleens and livers.

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Reproductive/Perinatal/Fetal Effects

The reportable events in this study were not statistically significant effects, but were visually observed dose-related trends suggesting possible biological significance. These potential biologically significant events are believed to be directly consequential to the overt maternal toxicity induced by MEKO administration as described previously, and are not considered indicative of primary reproductive toxicity. The parameters affected were:

1. F0 (for F1) prenatal mortality index slightly increased (not statistically significant) at 100 and 200 mg/kg/day relative to control (RTI Table 13);

2. F0 (for F1) stillbirth index slightly increased (not statistically significant) at 200 mg/kg/day relative to control (RTI Table 13);

3. F0 (for F1) live birth index slightly decreased (not statistically significant) at 200 mg/kg/day relative to control (RTI Table 13);

4. F1 four day survival index slightly decreased (not statistically significant) at 200 mg/kg/day relative to control due to the loss of one complete litter at this dose by postnatal day 2 (RTI Table 13);

5. F1 pup average bodyweights slightly decreased (not statistically significant) at 100 and 200 mg/kg/day relative to control (RTI Table 14);

F1 rebreed to produce F2b litters resulted in a small number of litters (n=2-4) per dose group. The following indices are based on these few litters:

6. F1 (for F2b) stillbirth index increased at 200 mg/kg/day relative to control (RTI Table 44);

7. F1 (for F2b) live birth index decreased at 200 mg/kg/day relative to control (RTI Table 44);

8. F1 (for F2b) 4 day survival index decreased at 100 and 200 mg/kg/day relative to control due to the demise of one dam with a live litter on postnatal day 3 (RTI Table 44);

9. F2b average pup body weight at 100 and 200 mg/kg/day was slightly decreased (not statistically significant) relative to control (RTI Table 45)

In summary, Akzo is making this submission under 8(e) because the reported data concerns reproductive toxicity; however, the Agency should note that Akzo believes that these data should not be interpreted as reflective of MEKO reproductive toxicity, but rather they should be considered as secondary to maternal toxicity. In fact, the NOAEL for reproductive and postnatal toxicity was considered by the author of the draft final report to be at least 200 mg/kg/day, the highest dose administered in this study. An adult NOAEL could not be determined due to histologic evidence of hepatic and splenic involvement at the lowest dose.

If there are questions regarding this submission, please contact Ed Bisinger at 312-906-7588.

Sincerely,

Edwin C. Bisinger Jr.

Edwin C. Bisinger
Manager, Product Regulation
and Toxicology

Attachments

cc: C. Donohue (cover letter only)
J. Carmine
J. Massari
J. Gerhart
Sponsors of the MEKO Section 4 Test Rule:

Industrial Health Foundation (IHF):	Wm. Rinehart
Allied-Signal, Inc.:	M. Derelanko
Huls America, Inc.:	J. Hodgson
Aceto Corporation:	R. Goodman
Dussek Campbell, Ltd.:	A. Kotel
Troy Chemical Co.:	A. Krygsman
Mooney Chemicals Inc.:	M. Scott

Attachment 1
January 23, 1992

RTI TABLE 13 -- FC Reproductive and Lactational Indices

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Table 13. F_0 Reproductive and Lactational Indexes for the Methyethyl Ketoxime Two Generation Reproductive Toxicity Study

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
No. of Animals Started on Study:				
Males	30	30	30	30
Females	30	30	30	30
No. of Females Paired	30	30	30	19
No. of Sperm Positive Females	27	29	29	17
Mating Index (no. sperm positive/no. mated)	90.0	96.7	96.7	89.5
No. of Pregnant Females	27	28	29	17
Fertility Index (no. pregnant/no. sperm positive)	100.0	96.6	100.0	100.0
No. Males Paired	30	30	30	24
No. of Males Impregnating Females	27	28	26	18
Mating Index (no. males impregnating females/no. males paired)	90.0	93.3	86.7	75.0

(continued)

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Table 13. F_0 Reproductive and Lactational Indexes (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
No. of Males Siring Litters	27	26	26	17
Fertility Index (no. males siring litters/no. males impregnating females)	100.0	92.9	100.0	94.4
No. of Females with Live Litters (pnd 0)	27	28	29	16
Gestational Index (no. live litters/no. pregnant)	100.0	100.0	100.0	94.1
Gestational Length (days)[a]	22.3 ± 0.1 N=27	22.5 ± 0.1 N=28	22.3 ± 0.1 N=29	22.3 ± 0.1 N=17
Number of Implantation Sites per Female[a]	15.6 ± 0.6 N=27	14.6 ± 0.7 N=28	15.2 ± 0.5 N=29	15.8 ± 1.0 N=17
Number of Live Pups per Litter on Postnatal Day 0[a]	14.9 ± 0.5 N=27	14.2 ± 0.7 N=28	13.5 ± 0.6 N=29	14.1 ± 1.3 N=17

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Table 13. F_0 Reproductive and Lactational Indexes (continued)

	Methylethylenetoxime (mg/kg/day, po)			
	0	10	100	200
Number of Dead Pups per Litter on Postnatal Day 0[a]				
	0.1 ± 0.1 N=27	0.3 ± 0.1 N=28	0.3 ± 0.1 N=29	0.5 ± 0.5 N=17
Total Number of Pups per Litter on Postnatal Day 0[a]				
	15.0 ± 0.5 N=27	14.5 ± 0.7 N=28	13.8 ± 0.7 N=29	14.6 ± 1.0 N=17
No. of Live Litters:				
Postnatal Day 0	27	28	29	16
Postnatal Day 4	27	28	29	15
Postnatal Day 7	27	28	29	15
Postnatal Day 14	27	28	29	15
Postnatal Day 21	27	28	29	15
Prenatal Mortality Index (no. implants-no. live/no. implants)[a]				
	8.0 ± 1.4 N=27	7.0 ± 2.1 N=28	13.1 ± 3.1 N=29	15.6 ± 6.2 N=17
Stillbirth Index (no. dead at birth/total no. born)[a]				
	0.7 ± 0.4 N=27	2.3 ± 1.0 N=28	1.8 ± 0.9 N=29	6.2 ± 5.9 N=17

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Table 13. F_0 Reproductive and Lactational Indexes (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Live Birth Index (no. live at birth/total no. born)[a]				
	99.3	97.7	98.2	93.8
	± 0.4	± 1.0	± 0.9	± 5.9
	N=27	N=28	N=29	N=17
4 Day Survival Index (no surviving 4 days/no. live at birth)[a]				
	99.3	97.2	97.5	91.2
	± 0.4	± 0.9	± 0.9	± 6.2
	N=27	N=28	N=29	N=16
7 Day Survival Index (no. surviving 7 days/no. live day 4)[a]				
	98.6	98.2	99.1	98.3
	± 0.8	± 0.8	± 0.9	± 1.7
	N=27	N=28	N=29	N=15
14 Day Survival Index (no. surviving 14 days/no. live day 7)[a]				
	100.0	99.6	99.4	100.0
	± 0.0	± 0.4	± 0.6	± 0.0
	N=27	N=28	N=29	N=15
21 Day Survival Index (no. surviving 21 days/no. live day 14)[a]				
	100.0	100.0	100.0	100.0
	± 0.0	± 0.0	± 0.0	± 0.0
	N=27	N=28	N=29	N=15
Lactational Index (no. surviving 21 days/no. live day 4)[a]				
	98.6	97.8	98.7	98.3
	± 0.8	± 0.9	± 1.3	± 1.7
	N=27	N=28	N=29	N=15

[a]Reported as the mean ± S.E.M. All indexes are the average percent per litter.
[b]$p<0.05$; Test for Linear Trend on Proportions.

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Attachment 2
January 23, 1992

RTI TABLE 14 -- Litter Size and Body Weights for F1 Offspring During the Postnatal Period

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Table 14. Litter Size and Body Weights for the F_1 Offspring During the Postnatal Period for the Methylethyl Ketoxime Two Generation Reproductive Toxicity Study

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Number of Pups per Litter (pnd 0)[a]	14.9 ± 0.5 N=27	14.2 ± 0.7 N=28	13.5 ± 0.6 N=29	14.9 ± 1.0 N=16
Average Number of Pups per Litter (pnd 1)[a]	14.9 ± 0.5 N=27	14.0 ± 0.7 N=28	13.3 ± 0.6 N=29	13.8 ± 1.3 N=16
Average Number of Pups per Litter (pnd 4)[a]	14.8 ± 0.5 N=27	13.8 ± 0.7 N=28	13.2 ± 0.6 N=29	14.4 ± 1.0 N=15
Average Number of Pups per Litter (pnd 7)[a]	7.9 ± 0.1 N=27	7.7 ± 0.1 N=28	7.8 ± 0.1 N=29	7.5 ± 0.4 N=15
Average Number of Pups per Litter (pnd 14)[a]	7.9 ± 0.1 N=27	7.6 ± 0.1 N=28	7.8 ± 0.1 [illegible]	7.5 ± 0.4 N=15
Average Number of Pups per Litter (pnd 21)[a]	7.9 ± 0.1 N=27	7.6 ± 0.1 N=28	7.8 ± 0.1 N=29	7.5 ± 0.4 N=15

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Table 14. Litter Size and Body Weights for the F_1 Offspring (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Pup Body Weight (g) per Litter (pnd 1)[a]				
	7.12	6.95	6.38	6.76
	± 0.13	± 0.18	± 0.12	± 0.26
	N=27	N=28	N=28	N=16
Average Male Body Weight (g) per Litter (pnd 1)[a]				
	7.31	7.10	7.07	7.08
	± 0.14	± 0.19	± 0.13	± 0.23
	N=27	N=28	N=28	N=15
Average Female Body Weight (g) per Litter (pnd 1)[a]				
	6.90	6.78	6.7[illegible]	6.62
	± 0.12	± 0.18	± 0.1[illegible]	± 0.24
	N=27	N=28	N=28	N=16
Average Pup Body Weight (g) per Litter (pnd 4)[a]				
	10.25	10.15	9.7[illegible]	9.47
	± 0.27	± 0.35	± 0.26	± 0.37
	N=27	N=28	N=29	N=15
Average Male Body Weight (g) per Litter (pnd 4)[a]				
	10.57	10.39	9.[illegible]	9.73
	± 0.28	± 0.39	± 0.28	± 0.39
	N=27	N=28	N=29	N=15
Average Female Body Weight (g) per Litter (pnd 4)[a]				
	9.89	9.88	9.47	9.21
	± 0.25	± 0.34	± 0.27	± 0.36
	N=27	N=28	N=29	N=15

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Table 14. Litter Size and Body Weights for the F_1 Offspring (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Pup Body Weight (g) per Litter (pnd 7)[a]				
	16.48 ± 0.36 N=27	16.01 ± 0.53 N=28	15.63 ± 0.39 N=29	15.03 ± 0.74 N=15
Average Male Body Weight (g) per Litter (pnd 7)[a]				
	17.11 ± 0.38 $ N=27	16.36 ± 0.58 N=28	15.94 ± 0.42 N=29	15.38 ± 0.79 N=15
Average Female Body Weight (g) per Litter (pnd 7)[a]				
	15.79 ± 0.35 N=27	15.64 ± 0.53 N=28	15.34 ± 0.39 N=29	14.67 ± 0.72 N=15
Average Pup Body Weight (g) per Litter (pnd 14)[a]				
	33.81 ± 0.55 $ N=26	33.67 ± 0.84 N=28	32.46 ± 0.71 N=29	30.85 ± 1.31 N=15
Average Male Body Weight (g) per Litter (pnd 14)[a]				
	34.68 ± 0.65 $ N=26	34.10 ± 0.88 N=28	32.93 ± 0.81 N=29	31.93 ± 1.20 N=15
Average Female Body Weight (g) per Litter (pnd 14)[a]				
	32.81 ± 0.47 $$ N=26	33.18 ± 0.85 N=28	32.09 ± 0.67 N=29	29.77 ± 1.49 N=15

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Table 14. Litter Size and Body Weights for the F_1 Offspring (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Pup Body Weight (g) per Litter (pnd 21)[a]	53.75 ± 0.92 $ N=27	53.08 ± 1.46 N=27	51.32 ± 0.87 N=29	49.23 ± 1.98 N=15
Average Male Body Weight (g) per Litter (pnd 21)[a]	55.20 ± 1.04 $ N=27	54.00 ± 1.58 N=27	52.32 ± 1.05 N=29	50.33 ± 2.07 N=15
Average Female Body Weight (g) per Litter (pnd 21)[a]	52.15 ± 0.84 $ N=27	52.20 ± 1.44 N=27	50.53 ± 0.83 N=29	48.12 ± 2.02 N=15
Percent Male Pups per Litter (pnd 1)[a]	49.5 ± 2.5 N=27	47.4 ± 2.1 N=28	5[illegible].1 ± 2.5 N=28	48.6 ± [illegible].2 N=16
Percent Male Pups per Litter (pnd 4)[a]	50.8 ± 2.8 N=27	47.0 ± 2.5 N=28	52.8 ± 2.5 N=29	50.5 ± 2.6 N=15
Percent Male Pups per Litter (pnd 7)[a]	50.6 ± 1.6 N=27	49.0 ± 1.2 N=28	48.8 ± [illegible] N=29	51.1 ± 1.1 N=15

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Table 14. Litter Size and Body Weights for the F_1 Offspring (concluded)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Percent Male Pups per Litter (pnd 14)[a]	50.6 ± 1.6 N=26	49.2 ± 1.2 N=28	48.4 ± 1.6 N=29	51.1 ± 1.1 N=15
Percent Male Pups per Litter (pnd 21)[a]	50.6 ± 1.6 N=27	49.7 ± 1.2 N=27	48.4 ± 1.6 N=29	51.1 ± 1.1 N=15

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
$p<0.05; Test for Linear Trend.
$$p<0.01; Test for Linear Trend.

Attachment 3
January 23, 1992

RTI TABLE 44 -- F1 Reproductive and Lactational Indices of the F2b Litters

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Table 4. F_1 Reproductive and Lactational Indexes of the F_{2b} Litters for the Methylethyl Ketoxime Two Generation Reproductive Toxicity Study

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
No. of Females Paired	16	12	11	6
No. of Sperm Positive Females	5	4[a]	5	4
Mating Index (no. sperm positive/no. mated)	31.3	33.3	45.5	66.7
No. of Pregnant Females	2	4	4	3
Fertility Index (no. pregnant/no. sperm positive)	40.0	100.0	80.0	75.0
No. of Males Paired	15	14	11	4
No. of Males Impregnating Females	4	4	5	3
Mating Index (no. of males impregnating females/no. of males paired)	26.7	28.6	45.5	75.0
No. of Males Siring Litters	2	4	4	2
Fertility Index (no. of males siring litters/no. of males impregnating females)	50.0	100.0	80.0	66.7

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Table 44. F_1 Reproductive and Lactational Indexes of the F_{2b} Litters (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Gestational Length (days)[b]	22.5 ± 0.5 N=2	23.0 ± 0.0 N=4	22.0 ± 0.0 N=2	23.7 ± 0.7 N=3
Number of Implantation Sites per Female[b]	17.0 ± 4.0 N=2	14.5 ± 2.9 N=4	12.5 ± 4.3 N=4	15.3 ± 0.9 N=3
Number of Live Pups per Litter on Postnatal Day 0[b]	12.5 ± 7.5 N=2	13.5 ± 2.8 N=4	13.7 ± 2.3 N=3	9.3 ± 4.1 N=3
Number of Dead Pups per Litter on Postnatal Day 0[b]	0.0 ± 0.0 N=2	0.5 ± 0.3 N=4	0.3 ± 0.3 N=3	2.7 ± 2.7 N=3
Total Number of Pups per Litter on Postnatal Day 0[b]	12.5 ± 7.5 N=2	14.0 ± 3.0 N=4	14.0 ± 2.6 N=3	12.0 ± 2.6 N=3
No. of Females with Live Litters (pnd 0)	2	4	3	3
Gestational Index (no. live litters/no. pregnant)	100.0	100.0	75.0	100.0

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Table 44. F_1 Reproductive and Lactational Indexes of the F_{2b} Litters (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
No. of Live Litters:				
Postnatal Day 0	2	4	3	3
Postnatal Day 4	2	4	3	2[c]
Postnatal Day 7	2	4	2	2
Postnatal Day 14	2	4	2	2
Postnatal Day 21	2	4	2	2
Prenatal Mortality Index (no. implants-no. live/no. implants)[b]				
	31.2	8.1[a]	36.7	41.0
	± 21.4	± 4.7	± 21.3	± 23.1
	N=2	N=4	N=4	N=3
Stillbirth Index (no. dead at birth/total no. born)[b]				
	0.0	2.9	1.8	24.2
	± 0.0	± 1.7	± 1.8	± 24.2
	N=2	N=4	N=3	N=3
Live Birth Index (no. live at birth/total no. born)[b]				
	100.0	97.1	98.2	75.8
	± 0.0	± 1.7	± 1.8	± 24.2
	N=2	N=4	N=3	N=3
4 Day Survival Index (no. surviving 4 days/no. live at birth)[b]				
	100.0	93.9	81.5	66.7
	± 0.0	± 3.5	± 18.5	± 33.3
	N=2	N=4	N=3	N=3

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Table 44. F_1 Reproductive and Lactational Indexes of the F_{2b} Litters (concluded)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
7 Day Survival Index (no. surviving 7 days/no. live day 4)[b]	100.0 ± 0.0 N=2	96.9 ± 3.1 N=4	66.7 ± 33.3 N=3	100.0 ± 0.0 N=2
14 Day Survival Index (no. surviving 14 days/no. live day 7)[b]	100.0 ± 0.0 N=2	96.4 ± 3.6 N=4	100.0 ± 0.0 N=2	100.0 ± 0.0 N=2
21 Day Survival Index (no. surviving 21 days/no. live day 14)[b]	100.0 ± 0.0 N=2	100.0 ± 0.0 N=4	100.0 ± 0.0 N=2	100.0 ± 0.0 N=2
Lactational Index (no. surviving 21 days/no. live day 4)[b]	100.0 ± 0.0 N=2	93.8 ± 6.3 N=4	66.7 ± 33.3 N=3	100.0 ± 0.0 N=2

[a]One dam had implant sites, but was not included since we didn't know which breed (a or b) they were the result of.
[b]Reported as the mean ± S.E.M. All indexes are the average percent per litter.
[c]One dam was sacrificed in extremis on postnatal day 3.

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Attachment 4
January 23, 1992

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RTI TABLE 45 -- Litter Size and Body Weights for the F2b
Offspring During the Postnatal Period

Table 45. Litter Size and Body Weights for the F_{2b} Offspring During the Postnatal Period for the Methylethyl Ketoxime Two Generation Reproductive Toxicity Study

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Number of Pups per Litter (pnd 0)[a]	12.5 ± 7.5 N=2	13.5 ± 2.8 N=4	13.7 ± 2.3 N=3	9.3 ± 4.1 N=3
Average Number of Pups per Litter (pnd 1)[a]	12.5 ± 7.5 N=2	12.5 ± 2.5 N=4	13.7 ± 2.3 N=3	8.3 ± 4.4 N=3
Average Number of Pups per Litter (pnd 4)[a]	12.5 ± 7.5 N=2	12.5 ± 2.5 N=4	10.3 ± 1.5 N=3	6.7 ± 5.2 N=3
Average Number of Pups per Litter (pnd 7)[a]	6.5 ± 1.5 N=2	7.0 ± 0.7 N=4	5.3 ± 2.7 N=3	3.7 ± 2.3 N=3
Average Number of Pups per LItter (pnd 14)[a]	6.5 ± 1.5 N=2	6.8 ± 0.8 N=4	5.3 ± 2.7 N=3	3.7 ± 2.3 N=3
Average Number of Pups per Litter (pnd 21)[a]	6.5 ± 1.5 N=2	6.8 ± 0.8 N=4	5.3 ± 2.7 N=3	3.7 ± 2.3 N=3

(continued)

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Table 45. Litter Size and Body Weights for the F_{2b} Offspring During the Postnatal Period (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Pup Body Weight (g) per Litter (pnd 1)[a]				
	7.54 ± 1.50 N=2	6.83 ± 0.42 N=4	7.09 ± 0.82 N=3	6.60 ± 0.47 N=3
Average Male Body Weight (g) per Litter (pnd 1)[a]				
	7.73 ± 1.46 N=2	7.10 ± 0.49 N=4	7.24 ± 0.80 N=3	6.64 ± 0.50 N=3
Average Female Body Weight (g) per Litter (pnd 1)[a]				
	7.14 ± 1.31 N=2	6.65 ± 0.48 N=4	6.80 ± 0.75 N=3	6.85 ± 0.50 N=2
Average Pup Body Weight (g) per Litter (pnd 4)[a]				
	11.77 ± 3.23 N=2	9.97 ± 1.01 N=4	9.31 ± 2.58 N=3	10.95 ± 0.42 N=2
Average Male Body Weight (g) per Litter (pnd 4)[a]				
	12.02 ± 3.38 N=2	10.46 ± 1.11 N=4	9.43 ± 2.61 N=3	11.30 ± 0.29 N=2
Average Female Body Weight (g) per Litter (pnd 4)[a]				
	10.91 ± 2.49 N=2	9.62 ± 1.11 N=4	9.01 ± 2.39 N=3	10.32 ± 0.75 N=2

(continued)

Table 45. Litter Size and Body Weights for the F_{2b} Offspring During the Postnatal Period (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Pup Body Weight (g) per Litter (pnd 7)[a]				
	18.99 ± 4.36 N=2	18.76 ± 2.91 N=4	23.30 ± 7.49 N=2	17.73 ± 1.88 N=2
Average Male Body Weight (g) per Litter (pnd 7)[a]				
	19.30 ± 4.18 N=2	19.75 ± 2.88 N=4	23.55 ± 7.63 N=2	18.11 ± 1.58 N=2
Average Female Body Weight (g) per Litter (pnd 7)[a]				
	18.49 ± 4.36 N=2	17.78 ± 3.06 N=4	22.66 ± 6.96 N=2	17.02 ± 2.52 N=2
Average Pup Body Weight (g) per Litter (pnd 14)[a]				
	40.56 ± 4.56 N=2	37.15 ± 3.16 N=4	38.32 ± 4.32 N=2	37.60 ± 3.55 N=2
Average Male Body Weight (g) per Litter (pnd 14)[a]				
	41.02 ± 4.21 N=2	39.77 ± 2.75 N=4	38.55 ± 4.48 N=2	38.24 ± 3.66 N=2
Average Female Body Weight (g) per Litter (pnd 14)[a]				
	39.94 ± 4.74 N=2	34.92 ± 4.02 N=4	37.70 ± 3.75 N=2	36.69 ± 3.69 N=2

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Table 45. Litter Size and Body Weights for the F_{2b} Offspring During the Postnatal Period (continued)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Average Pup Body Weight (g) per Litter (pnd 21)[a]	64.14 ± 10.80 N=2	60.44 ± 4.97 N=4	60.79 ± 5.90 N=2	60.08 ± 3.81 N=2
Average Male Body Weight (g) per Litter (pnd 21)[a]	64.76 ± 10.31 N=2	64.44 ± 5.02 N=4	61.90 ± 5.82 N=2	62.32 ± 3.37 N=2
Average Female Body Weight (g) per Litter (pnd 21)[a]	63.31 ± 11.09 N=2	57.34 ± 5.88 N=4	58.63 ± 4.94 N=2	56.50 ± 5.59 N=2
Percent Male Pups per Litter (pnd 1)[a]	65.0 ± 15.0 N=2	43.7 ± 9.3 N=4	63.1 ± 8.4 N=3	75.2 ± 12.6 N=3
Percent Male Pups per Litter (pnd 4)[a]	65.0 ± 15.0 N=2	43.7 ± 9.3 N=4	57.1 ± 12.4 N=3	62.7 ± 3.9 N=2
Percent Male Pups per Litter (pnd 7)[a]	65.0 ± 15.0 N=2	44.3 ± 8.3 N=4	62.5 ± 12.5 N=2	58.3 ± 8.3 N=2

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Table 45. Litter Size and Body Weights for the F_{2b} Offspring During the Postnatal Period (concluded)

	Methylethyl Ketoxime (mg/kg/day, po)			
	0	10	100	200
Percent Male Pups per Litter (pnd 14)[a]	65.0 ± 15.0 N=2	42.5 ± 7.5 N=4	62.5 ± 12.5 N=2	58.3 ± 8.3 N=2
Percent Male Pups per Litter (pnd 21)[a]	65.0 ± 15.0 N=2	42.5 ± 7.5 N=4	62.5 ± 12.5 N=2	58.3 ± 8.3 N=2

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.

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