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89-900000426 : DCN

September 20, 1990

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

Re: Notice of Substantial Risk Under TSCA 8(e) for Methylene-  
ketoxime (MEKO) when Administered by Gavage to Rabbits in a  
Developmental Toxicity Study

Dear Sir/Madame:

Akzo Chemicals Inc. (ACI) submits this notification in accordance with Section 3(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. Register 54(176), 37799, September 13, 1990]. This study was intended to evaluate the developmental toxicity potential of MEKO when administered to rabbits by oral gavage during the period of major organogenesis.

Accordingly, ACI is advising the EPA of preliminary and unaudited results of a definitive developmental toxicity study in New Zealand White Rabbits at Springborn Laboratories (Study No. 32245) in which groups of 18 artificially inseminated rabbits were administered either 0, 8, 14, 24 or 40 mg/kg MEKO in distilled water on gestation days 6-18. Control rabbits were administered distilled water only. Body weight and food consumption were recorded throughout the study. Does were euthanized and received a Cesarean-section and gross necropsy on gestation day 29. Their uterine contents were counted, weighed and examined. All fetuses received a gross external morphological examination, a visceral examination and a skeletal examination. To date, visceral and skeletal data have not yet been summarized.

Akzo Chemicals Inc.  
300 South Riverside Plaza  
Chicago, Illinois 60606  
Tel. (312) 906 7500  
Fax (312) 906 7680

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In this study, statistically significant decreases (Attachment 1) in body weight and food consumption parameters were seen in the 40 mg/kg/day dose group. The 24 mg/kg/day dose group displayed decreased food consumption on a single day at mid-study only. Salient maternal toxicity was observed in the 40 mg/kg/day dosage group where 8 does died and 3 aborted (Attachment 2). Finally, statistically significant decreases in viable fetuses were observed in both the 24 and 40 mg/kg/day dosage groups, while an increase in early resorptions was observed in the 40 mg/kg/day dosage group only (see Attachment 2).

Akzo is making this submission under 8(e) because the reported data concerns developmental toxicity. However, Akzo believes that these data are reflective of biological variation and/or maternal toxicity:

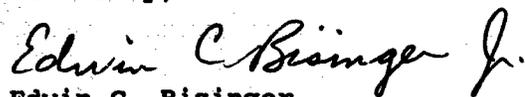
1. statistically significant changes which occurred at 40 mg/kg/day occurred at a grossly maternally toxic dosage level, a dosage which killed 8 does (Attachment 1);
2. statistically significant and decreased viable fetus means of 5.3 and 4.7 for the 24 and 40 mg/kg/day dose groups, respectively, fall within the range of the laboratory's historical control data ( $\bar{x}$  = 7.1; range = 4.6 - 9.1; Attachment 3);
3. the increase in the 40 mg/kg/day mean for (early) resorptions (1.7) is totally reflected in the study's postimplantation loss value of 1.7, which is not statistically significant in this study and within the laboratory's historical control data range ( $\bar{x}$  = 0.7; range = 0.2 - 1.9; Attachment 3);
4. similar effects were NOT observed at a similar dosage level in a range-finding study (Attachment 4);
5. the means in the 40 mg/kg/day dose group are artifacts of a low number of litters (N=6), an insignificant number of litters to evaluate statistically (Attachment 1);
6. fetal body weight (Attachment 2), a less variable parameter than fetal viability or resorption parameters, suggested an ABSENCE of MEKO developmental toxicity.

Page 3 of 3  
September 20, 1990

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

Sincerely,



Edwin C. Bisinger  
Manager, Product Regulation  
and Toxicology

Attachments

cc: C. Donohue (cover letter only)  
J. Carmine (cover letter only)  
J. Massari (cover letter only)  
J. Gerhart

External Distribution (Industrial Health Foundation MEKO Toxicology Committee Members):

Industrial Health Foundation (IHF):	Wm. Rinehart, MEKO Toxicology Coordinator
Allied-Signal, Inc.:	Michael Derelanko, MEKO Toxicology Chairman
Huls America, Inc.:	J. Hodgson
Aceto Corporation:	Roy Goodman
Dussek Campbell, Ltd.:	Alex Kotel
Troy Chemical Co.:	Adrian Krygsman
Mooney Chemicals Inc.:	Michael Scott

4

Attachment 1  
September 26, 1990

ATTACHMENT 1: GENERAL TOXICOLOGY DATA SUMMARIES  
OF MEKO TERATOLOGY STUDY IN RABBITS

- ABSOLUTE BODY WEIGHT
- BODY WEIGHT GAIN
- FOOD CONSUMPTION

SLS STUDY NO.: 32245  
 CLIENT: IBF

**TABIZ 1**  
**TERATOLOGY STUDY IN RABBITS WITH MEKO**  
**SUMMARY OF SURVIVAL AND PREGNANCY**

10:48 10-JUL-90 PAGE 1

GROUP : LEVEL :	1 0 MG/KG/DAY		2 8 MG/KG/DAY		3 14 MG/KG/DAY		4 24 MG/KG/DAY		5 40 MG/KG/DAY	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	18		18		18		18		18	
FEMALES THAT ABORTED OR DELIVERED	0	0.0	0	0.0	0	0.0	0	0.0	3	16.7
FEMALES THAT DIED FEMALES THAT ABORTED NONGRAVID GRAVID	0	0.0	0	0.0	0	0.0	0	0.0	8	44.4
FEMALES EXAMINED AT SCHEDULED NECROPSY NONGRAVID GRAVID	18	100.0	18	100.0	18	100.0	18	100.0	7	38.9
WITH RESORPTIONS ONLY WITH VIABLE FETUSES	1	5.6	1	5.6	3	16.7	7	38.9	1	14.3
	17	94.4	17	94.4	15	83.3	11	61.1	6	85.7
	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	17	100.0	17	100.0	15	100.0	11	100.0	6	100.0
TOTAL FEMALES GRAVID	17	94.4	17	94.4	15	83.3	11	61.1	16	88.9

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5

TABLE 3  
 TERATOLOGY STUDY IN RABBITS WITH MEKO  
 SUMMARY OF GESTATION BODY WEIGHT DATA (GRAMS)

DAY	GROUP :	LEVEL :	MG/KG/DAY				
			0	8	14	24	40
			1	2	3	4	5
DAY 6	MEAN		3410	3414	3387	3494	3432
	S.D.		231.3	192.3	215.3	199.0	220.9
	N		17	17	15	11	16
DAY 9	MEAN		3719	3710	3659	3793	3679
	S.D.		278.2	235.3	282.1	213.4	277.3
	N		17	17	15	11	16
DAY 12	MEAN		3766	3770	3690	3802	3673
	S.D.		276.0	225.9	287.8	193.0	277.2
	N		17	17	15	11	16
DAY 15	MEAN		3813	3838	3732	3755	3390**
	S.D.		287.6	236.8	300.5	195.0	423.0
	N		17	17	15	11	13
DAY 19	MEAN		3923	3918	3814	3861	3538**
	S.D.		297.2	263.5	300.1	200.5	409.9
	N		17	17	15	11	10
DAY 24	MEAN		3999	3977	3858	3979	3774
	S.D.		292.6	316.4	332.7	204.4	322.7
	N		17	17	15	11	9
DAY 29	MEAN		4068	4069	3918	4062	3955
	S.D.		297.5	328.9	357.5	242.7	323.8
	N		17	17	15	11	6
DAY 29	MEAN		4139	4130	3932	4105	4088
	S.D.		327.7	361.6	321.1	267.0	362.6
	N		17	17	15	11	6

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6

SIGNIFICANTLY DIFFERENT FROM CONTROL: \*\* - P<0.01

SLS STUDY NO.: 3224 5  
 CLIENT: IHF

TABLE 4  
 TERATOLOGY STUDY IN RABBITS WITH MEKO  
 SUMMARY OF GESTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP :	1	2	3	4	5
LEVEL :	0 MG/KG/DAY	8 MG/KG/DAY	14 MG/KG/DAY	24 MG/KG/DAY	40 MG/KG/DAY
DAY 0- 6 MEAN	309	296	271	299	247
S.D.	124.3	87.7	106.2	85.8	109.0
N	17	17	15	11	16
DAY 6- 9 MEAN	47	61	31	9	-6*
S.D.	44.5	39.1	39.2	62.3	89.9
N	17	17	15	11	16
DAY 9- 12 MEAN	47	68	42	-47	-257**
S.D.	69.6	41.0	31.9	77.2	203.8
N	17	17	15	11	13
DAY 12- 15 MEAN	110	80	81	106	28
S.D.	75.7	53.4	25.5	42.6	144.7
N	17	17	15	11	10
DAY 15- 19 MEAN	76	59	44	118	165*
S.D.	53.2	77.3	59.2	99.0	58.6
N	17	17	15	11	9
DAY 19- 24 MEAN	69	92	60	83	136
S.D.	71.8	50.1	110.5	134.7	129.7
N	17	17	15	11	6
DAY 24- 29 MEAN	71	61	15	43	133
S.D.	88.6	71.3	209.6	62.2	59.0
N	17	17	15	11	6
DAY 6- 19 MEAN	280	267	199	186	117**
S.D.	108.4	144.0	97.2	68.7	190.0
N	17	17	15	11	9
DAY 19- 29 MEAN	140	153	75	126	269
S.D.	107.3	102.3	242.1	113.9	131.8
N	17	17	15	11	6

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7

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* P<0.05; \*\* = P<0.01

TABLE 5  
 TERATOLOGY STUDY IN RABBITS WITH MEXO  
 SUMMARY OF GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

SLS STUDY NO.: 3224 5 CLIENT: IHF	GROUP :				
	1 0 MG/KG/DAY	2 8 MG/KG/DAY	3 14 MG/KG/DAY	4 24 MG/KG/DAY	5 40 MG/KG/DAY
DAY 0- 6 MEAN	196	203	181	203	194
S.D.	27.8	22.2	28.2	19.0	22.5
N	17	17	15	11	16
DAY 6- 9 MEAN	193	190	168	180	156**
S.D.	28.8	26.0	33.3	30.0	34.1
N	17	17	15	11	16
DAY 9- 12 MEAN	177	184	154	128*	74**
S.D.	26.3	34.8	25.6	40.2	74.1
N	17	17	15	11	14
DAY 12- 15 MEAN	168	182	154	144	96**
S.D.	35.0	39.9	22.5	39.9	63.5
N	17	17	15	11	10
DAY 15- 19 MEAN	185	195	155	172	174
S.D.	49.0	93.3	35.0	27.0	47.5
N	17	17	15	11	9
DAY 19- 24 MEAN	161	179	136	182	200
S.D.	35.5	36.2	45.0	50.0	17.5
N	17	17	15	11	7
DAY 24- 29 MEAN	116	141	91	133	166
S.D.	44.3	48.7	41.0	38.5	30.4
N	17	17	15	11	6
DAY 6- 19 MEAN	161	186	157	157	138*
S.D.	31.8	40.3	27.0	26.7	40.7
N	17	17	15	11	9
DAY 19- 29 MEAN	139	161	113	158	184*
S.D.	34.3	27.5	37.8	40.4	22.8
N	17	17	15	11	6

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8

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P < 0.05; \*\* = P < 0.01

SLS STUDY NO.: 3224 5  
 CLIENT: IHP

TABLE 6  
 TERAUTOLOGY STUDY IN RABBITS WITH MEKO  
 SUMMARY OF GESTATION FOOD CONSUMPTION DATA (GRAMS/KG/DAY)

GROUP :	1	2	3	4	5
LEVEL :	0 MG/KG/DAY	8 MG/KG/DAY	14 MG/KG/DAY	24 MG/KG/DAY	40 MG/KG/DAY
DAY 0- 6 MEAN	55	57	51	56	54
S.D.	6.7	5.7	6.9	5.7	4.8
N	17	17	15	11	16
DAY 6- 9 MEAN	51	51	45	48	42**
S.D.	6.6	7.1	7.8	7.9	8.3
N	17	17	15	11	16
DAY 9- 12 MEAN	47	49	41	34*	20**
S.D.	5.3	9.2	5.1	10.9	19.3
N	17	17	15	11	14
DAY 12- 15 MEAN	43	47	41	38	26**
S.D.	7.7	9.5	4.3	9.9	16.4
N	17	17	15	11	10
DAY 15- 19 MEAN	47	49	40	44	47
S.D.	11.5	24.3	7.4	6.3	13.1
N	17	17	15	11	9
DAY 19- 24 MEAN	40	44	35	45	51*
S.D.	7.7	7.0	10.5	12.5	5.1
N	17	17	15	11	7
DAY 24- 29 MEAN	28	34	23	32	42*
S.D.	9.7	10.6	10.3	8.2	8.1
N	17	17	15	11	6
DAY 6- 19 MEAN	47	48	42	41	37*
S.D.	7.2	9.9	5.5	6.7	9.5
N	17	17	15	11	6
DAY 19- 29 MEAN	34	39	29	39	47**
S.D.	7.2	7.5	9.3	9.5	6.5
N	17	17	15	11	6

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9

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* - P < 0.05; \*\* - P < 0.01

10

Attachment 2  
September 20, 1990

ATTACHMENT 2: CESAREAN-SECTION AND REPRODUCTION DATA SUMMARIES  
OF MEKO TERATOLOGY STUDY IN RABBITS

SLS STUDY NO.: 3224 5  
 CLIENT: INF

TABLE 8  
 TERATOLOGY STUDY IN RABBITS WITH MEKO  
 SUMMARY OF CESAREAN SECTION DATA

GROUP :	1	2	3	4	5
LEVEL :	0 MG/KG/DAY	8 MG/KG/DAY	14 MG/KG/DAY	24 MG/KG/DAY	40 MG/KG/DAY
<b>FEMALES GRAVID</b>	17	17	15	11	6
<b>CORPORA LUTEA</b>	TOTAL 174 MEAN 10.2 S.D. 1.8	177 10.4 2.3	152 10.1 2.2	125 11.4 3.2	56 9.3 2.1
<b>IMPLANTATION SITES</b>	TOTAL 137 MEAN 8.1 S.D. 1.3	110 6.5 2.6	64 5.8 2.4	38 6.3 3.1	
<b>PRE-IMPLANTATION LOSS</b>	TOTAL 37 MEAN 2.2 S.D. 1.8	67 3.9 3.0	47 3.1 1.7	61 5.5 4.3	18 3.0 3.5
<b>VIABLE FETUSES</b>	TOTAL 132 MEAN 7.8 S.D. 1.2	108 6.4 2.5	97 6.5 2.5	58 5.3* 2.4	28 4.7* 2.1
<b>DEAD FETUSES</b>	TOTAL 0	0	0	0	0
<b>LATE RESORPTIONS</b>	TOTAL 3 MEAN 0.2 S.D. 0.4	1 0.1 0.2	0 0.0 0.0	0 0.0 0.0	0 0.0 0.0
<b>EARLY RESORPTIONS</b>	TOTAL 2 MEAN 0.1 S.D. 0.3	1 0.1 0.2	8 0.5 1.3	6 0.5 0.7	10 1.7* 1.9

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P<0.05

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11

SLS STUDY NO.: 3224 5  
 CLIENT: IHF

TABLE 3  
 TERATOLOGY STUDY IN RABBIT: VIB MEKO  
 SUMMARY OF CESAREAN SECTION DATA

GROUP :	1		2		4		5	
	0 MG/KG/DAY		8 MG/KG/DAY		16 MG/KG/DAY		40 MG/KG/DAY	
LEVEL :	5	56	2	50	6	29	10	13
POST-IMPLANTATION LOSS	MEAN	4.5	MEAN	3.4	MEAN	2.9	MEAN	2.5
	S.D.	1.5	S.D.	1.6	S.D.	1.8	S.D.	1.9
SEX M / F		76 / 56		58 / 50		43 / 4		15 / 13
		43.9		46.1		44.5		48.1
FETAL WEIGHT (G)	MEAN	5.0	MEAN	6.4	MEAN	9.3	MEAN	5.9
	S.D.		S.D.		S.D.		S.D.	

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

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12

13

Attachment 3  
September 20, 1990

**ATTACHMENT 3: SPRINGBORN LABORATORY HISTORICAL CONTROL  
DATA FOR TERATOLOGY STUDIES**

SPRINGDALE LABORATORIES, INC.  
SPENCERVILLE, OH 45927

HISTORICAL CONTROL DATA  
NEW ZEALAND WHITE RABBITS

CAESAREAN SECTION DATA

	TOTAL NO.	PERCENT
FEMALES ON STUDY/ NO. OF STUDIES	280/14	--
FEMALES THAT ABORTED OR DELIVERED	4	1.4
FEMALES THAT DIED	0	0
FEMALES EXAMINED AT SCHEDULED NECROPSY	276	98.6
NONGRAVID	29	10.5
GRAVID	247	89.5
WITH RESORPTIONS ONLY	3	1.2
WITH VIABLE FETUSES	242	87.7
TOTAL FEMALES GRAVID	251	93.8
	MEAN	RANGE OF MEANS LOW HIGH
CORPORA LUTEA	11.6	8.4 - 15.4
IMPLANTATION SITES	7.9	5.6 - 9.3
VIABLE FETUSES	7.1	4.6 - 9.1
MALES:FEMALES	828:892	
SEX RATIO M/F	0.928	
POST-IMPLANTATION LOSS	0.7	0.2 - 1.9
FETAL WEIGHT (G)	44.6	40.6 - 48.6

15

**Attachment 4**  
**September 20, 1990**

**ATTACHMENT 4: RANGE-FINDING TERATOLOGY STUDY IN RABBITS WITH MEKO;  
REPRODUCTION DATA SUMMARIES**

SLS STUDY NO.: 3224 2  
 CLIENT: IRP

TABLE 12  
 RANGE-FINDING TERATOLOGY STUDY IN RABBITS WITH MEKO  
 SUMMARY OF CESAREAN SECTION OBSERVATIONS

GROUP : LEVEL :	0 MG/KG/DAY					10 MG/KG/DAY					20 MG/KG/DAY					40 MG/KG/DAY					80 MG/KG/DAY				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
FEMALES GRAVID	4	3	5	2	a																				
CORPORA LUTEA	TOTAL 40 MEAN 10.0 S.D. 2.2	37 12.3 4.5	58 11.6 2.7	23 11.5 2.1																					
IMPLANTATION SITES	TOTAL 32 MEAN 8.0 S.D. 3.6	18 6.0 2.6	47 9.4 2.1	20 10.0 2.8																					
PRE-IMPLANTATION LOSS	TOTAL 8 MEAN 2.0 S.D. 2.8	19 6.3 3.2	11 2.2 4.4	3 1.5 0.7																					
VIABLE FETUSES	TOTAL 30 MEAN 7.5 S.D. 3.7	16 5.3 2.1	42 8.4 2.3	17 8.5 3.5																					
DEAD FETUSES	TOTAL 0	0	0	0																					
LATE RESORPTIONS	TOTAL 0 MEAN 0.0 S.D. 0.0	0 0.0 0.0	3 0.6 0.9	1 0.5 0.7																					
EARLY RESORPTIONS	TOTAL 2 MEAN 0.5 S.D. 1.0	2 0.7 1.2	2 0.4 0.5	2 1.0 1.4																					

\* ALL ANIMALS DEAD PRIOR TO SCHEDULED SACRIFICE

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16

SLS STUDY NO.: 3224 2  
CLIENT: IHV

TABLE 12  
RANGE-FINDING TERATOLOGY STUDY IN RABBITS WITH NIHO  
SUMMARY OF CESAREAN SECTION OBSERVATIONS

PAGE 2

GROUP : LEVEL :	DOSE (MG/KG/DAY)				
	0	10	20	40	80
TOTAL MEAN	0.5	0.7	1.0	1.5	1.5
S.D.	1.0	1.2	1.2	0.7	0.7
MEAN	42.3	51.8	41.7	39.5	39.5
S.D.	3.9	4.0	4.3	8.1	8.1

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\* ALL ANIMALS DEAD PRIOR TO SCHEDULED SACRIFICE

17

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