

FMC Corporation

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May 13, 1996



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ATTN: TSCA 8(e) Coordinator

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Dear Sir or Madam:

This notification is submitted on behalf of FMC Corporation ("FMC"), 1735 Market Street, Philadelphia, PA 19103, pursuant to Section 8(e) of the Toxic Substances Control Act, Public Law 94-469 ("TSCA") and the Statement of Interpretation and Enforcement Policy, 43 FR 11110-11116, March 16, 1978, as subsequently supplemented by EPA (the "Policy Statement").

On November 22, 1995, FMC Corporation informed the Agency of adverse effects observed during a 1-Generation Reproduction Study conducted in rats with Hydroxyphosphonoacetic acid, CAS Registry Number 23783-26-8. The specific reportable effect was the high level of mortality of females post parturition.

Continuing with this same study, FMC now wishes to notify the Agency of a further adverse finding: Hydroxyphosphonoacetic acid (HPA) was evaluated for potential reproductive toxicity in a one generation study. Groups of Sprague-Dawley rats were dosed orally by gavage for ten weeks prior to mating and throughout mating, gestation and lactation periods. Dose levels were 0, 1, 10, 50, 150 and 500 mg/kg/day.

The test material is a phosphonate and is expected to deplete calcium levels. Because the females were pregnant and had a higher calcium requirement for the developing fetuses and for the nursing pups, depletion of calcium stores may have contributed to the toxicity of the parents and the decreased viability/survival of the pups. During late gestation there were maternal deaths at the top two dose levels, reported previously in a TSCA 8(e) report. In the unaudited draft final report mean litter size (mean number of live pups

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per litter, Table 10) and survival (Viability Index, Table 11)) were lower among the offspring of the 500 mg/kg dose group than those of the control group. The mean litter size was slightly reduced among the offspring of the 150 mg/kg dose group (Table 10). Mean pup weights were similar to or slightly greater than mean control pup weights in the 150 and 500 mg/kg dose groups. These findings were considered to reflect the lower litter sizes (group mean litter weights, Table 12). High dose animals demonstrated clear evidence of toxicity, including mortality, necropsy findings among decedents, and broken incisors, reduced body weight gain among males and reduced food consumption among both sexes. The broken incisors and other necropsy findings are consistent with a depletion of calcium stores and known effects of HPA. Although the exact cause of the decreased litter size and survival are not known, the effects of HPA on calcium stores could have been a contributing factor.

As indicated in our November 22, 1995 letter, FMC makes no claims of confidentiality for this submission and a complete copy of the audited final report will be submitted once it becomes available.

Sincerely yours,



Linda M. Clark
Manager, Product Regulatory Affairs
215/299-6133

TABLE 10

HPA
One Generation Reproduction Study in Rats
Duration of Gestation and Overall Litter Performance

	Group/Dose Level (mg HPA.kg ⁻¹ .day ⁻¹)					
	1 (0)	2 (1)	3 (10)	4 (50)	5 (150)	6 (500)
Number Pregnant	23	22	22	24	21	22
Duration of Gestation (Days)						
21	7	4	5	7	4	1
22	12	14	15	12	14	13
23	4	3	2	5	1	2
26	0	1 ^c	0	0	0	0
Mean Duration (Days)	21.9	21.9	21.9	21.9	21.8	22.0
Number of females producing a live litter ^a	23	21	22	24	19	16
Gestation index as %	100	95	100	100	90	73
Mean number of implant sites ^d per pregnancy ± standard deviation	16.5 ± 2.8	16.2 ± 2.2	16.4 ± 2.5	15.5 ± 2.2	15.9 ± 3.2	15.8 ± 2.6
Mean number of implant sites ^b per pregnancy ± standard deviation	16.5 ± 3.0	16.0 ± 2.2	16.4 ± 2.5	15.3 ± 2.2	15.7 ± 3.2	14.8 ± 2.2
Mean total number of pups born ^b ± standard deviation	15.2 ± 3.2	14.8 ± 2.3	14.9 ± 2.4	14.1 ± 2.5	13.9 ± 3.1	13.2 ± 2.1
Mean number of live pups ^b per litter ± standard deviation:						
Day 0 of lactation	14.7 ± 3.7	14.5 ± 2.7	14.8 ± 2.4	13.9 ± 2.4	13.6 ± 3.2	12.4 ± 1.8
Day 1 of lactation	14.3 ± 3.7	14.2 ± 2.8	14.4 ± 2.1	13.2 ± 2.5	13.5 ± 3.1	11.8 ± 2.3
Day 4 of lactation	13.7 ± 3.5	13.1 ± 2.8	13.4 ± 2.6	12.7 ± 2.5	12.5 ± 2.8	10.5 ± 3.1
Day 7 of lactation	13.0 ± 3.4	12.6 ± 3.2	12.9 ± 2.4	12.6 ± 2.5	12.2 ± 3.0	9.8 ± 2.6
Day 14 of lactation	12.2 ± 3.4	12.1 ± 2.9	12.2 ± 2.6	11.7 ± 2.4	10.6 ± 3.7	9.0 ± 3.0
Day 21 of lactation	12.0 ± 3.5	11.9 ± 2.8	12.1 ± 2.6	11.6 ± 2.4	10.6 ± 3.8	8.9 ± 2.8

a = Includes premature decedents producing a live litter

b = Excludes litters where all pups died

c = Value for one premature decedent - excluded from mean calculation

d = Includes all pregnant animals

TABLE 11

HPA
One Generation Reproduction Study in Rats
Survival Indices

		Group/Dose Level (mg HPA.kg ⁻¹ .day ⁻¹)					
		1 (0)	2 (1)	3 (10)	4 (50)	5 (150)	6 (500)
Birth Index	Mean Litter Index (%)	92	93	93	92	90	85
	Number Losing >2 pups	3	2	3	4	4	5
	Number of Litters	21	16	21	21	17	11
Live Birth Index	Mean Litter Index (%)	95	98	97	98	97	95
	Number Losing >1 pup	2	2	1	2	1	3
	Number of Litters	21	17	21	23	17	11
Viability Index Days 0-4	Mean Litter Index (%)	96	91	91	93	94	84
	Number Losing >3 pups	3	1	1	4	1	3
	Number of Litters	21	17	21	23	17	11
Lactation Index Days 4-21	Mean Litter Index (%)	88	90	91	91	85	87
	Number Losing >1 pup	9	8	5	7	6	3
	Number of Litters	21	17	21	23	17	11
Overall Survival Index Birth-21	Mean Litter Index (%)	79	81	81	83	78	69
	Number Losing >4 pups	4	1	4	2	3	4
	Number of Litters	21	17	21	23	17	11

Means exclude litters where all pups died

TABLE 12

HPA
One Generation Reproduction Study in Rats
Group Mean Litter and Pup Weight (g) \pm Standard Deviation

Day of Lactation	Group/Dose Level (mg HPA.kg ⁻¹ .day ⁻¹)					
	1 (0)	2 (1)	3 (10)	4 (50)	5 (150)	6 (500)
LITTER						
Day 1	90 \pm 20	92 \pm 16	92 \pm 17	89 \pm 19	88 \pm 15	78 \pm 16
Day 4	125 \pm 33	125 \pm 30	126 \pm 32	128 \pm 34	121 \pm 28	97 \pm 38
Day 7	183 \pm 47	183 \pm 49	184 \pm 44	189 \pm 46	175 \pm 43	141 \pm 50
Day 14	341 \pm 75	353 \pm 80	351 \pm 64	352 \pm 62	312 \pm 93	273 \pm 88
Day 21	567 \pm 135	583 \pm 132	581 \pm 106	576 \pm 107	521 \pm 156	466 \pm 152
Mean of Litter Mean Pup Weight						
MALES						
Day 1	6.6 \pm 1.0	6.7 \pm 0.8	6.6 \pm 0.7	7.0 \pm 0.9	6.8 \pm 0.8	6.7 \pm 0.8
Day 4	9.6 \pm 2.1	9.8 \pm 1.9	9.5 \pm 1.7	10.3 \pm 1.9	10.2 \pm 2.1	9.2 \pm 2.1
Day 7	14.6 \pm 3.1	14.9 \pm 2.8	14.6 \pm 2.4	15.3 \pm 2.5	15.2 \pm 3.3	14.4 \pm 2.7
Day 14	29.5 \pm 5.5	30.5 \pm 4.1	29.8 \pm 3.6	31.1 \pm 3.8	31.1 \pm 7.1	31.6 \pm 2.3
Day 21	49.6 \pm 9.7	50.9 \pm 7.1	49.9 \pm 6.7	51.7 \pm 5.5	52.4 \pm 11.2	53.7 \pm 7.9
FEMALES						
Day 1	6.3 \pm 0.9	6.3 \pm 0.8	6.2 \pm 0.9	6.6 \pm 1.0	6.4 \pm 0.8	6.5 \pm 0.9
Day 4	9.2 \pm 2.0	9.3 \pm 1.9	9.3 \pm 1.7	9.6 \pm 1.9	9.5 \pm 1.9	9.0 \pm 2.3
Day 7	14.0 \pm 2.8	14.2 \pm 3.2	14.2 \pm 2.2	14.8 \pm 2.7	14.1 \pm 3.0	14.0 \pm 2.7
Day 14	28.3 \pm 5.2	28.7 \pm 5.0	28.6 \pm 3.6	29.8 \pm 4.9	29.6 \pm 6.4	29.4 \pm 3.6
Day 21	47.9 \pm 8.8	48.3 \pm 7.4	47.9 \pm 6.8	49.1 \pm 9.1	49.3 \pm 10.2	50.6 \pm 7.3

Means exclude litters where all pups died
Groups 1-5 means are based on 17 to 23 litters
Group 6 means are based on 11 litters