

Dimethylaminoethanol Bitartrate (DMAE)

*NTP Technical Report on the Prenatal Developmental Toxicity Studies of
Dimethylaminoethanol Bitartrate in Sprague Dawley (Hsd: Sprague Dawley SD) Rats
(Gavage Studies)*

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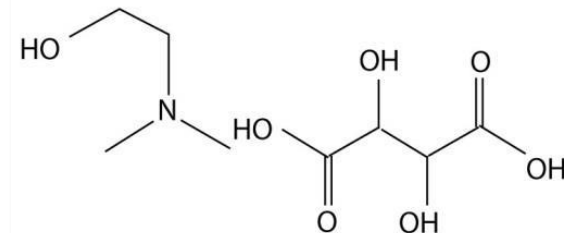
Peer-Review Meeting
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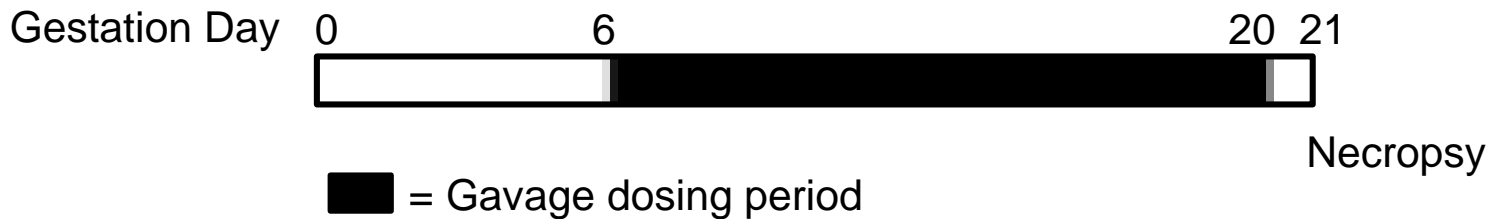
Dimethylaminoethanol Bitartrate (DMAE)

- Close structural analog of choline, an essential nutrient
- Dietary supplements are marketed to improve memory and general cognitive function due to the ability of DMAE to increase levels of acetylcholine in the brain
- Exposure may also occur through occupational and industrial routes (e.g., spray painting, beverage can lacquering)
- **Study Rationale:** Concerns for widespread human exposure through its use in industrial and consumer products
 - Limited literature indicating may be a teratogen and reproductive toxicant





Dose Range-Finding Study Design

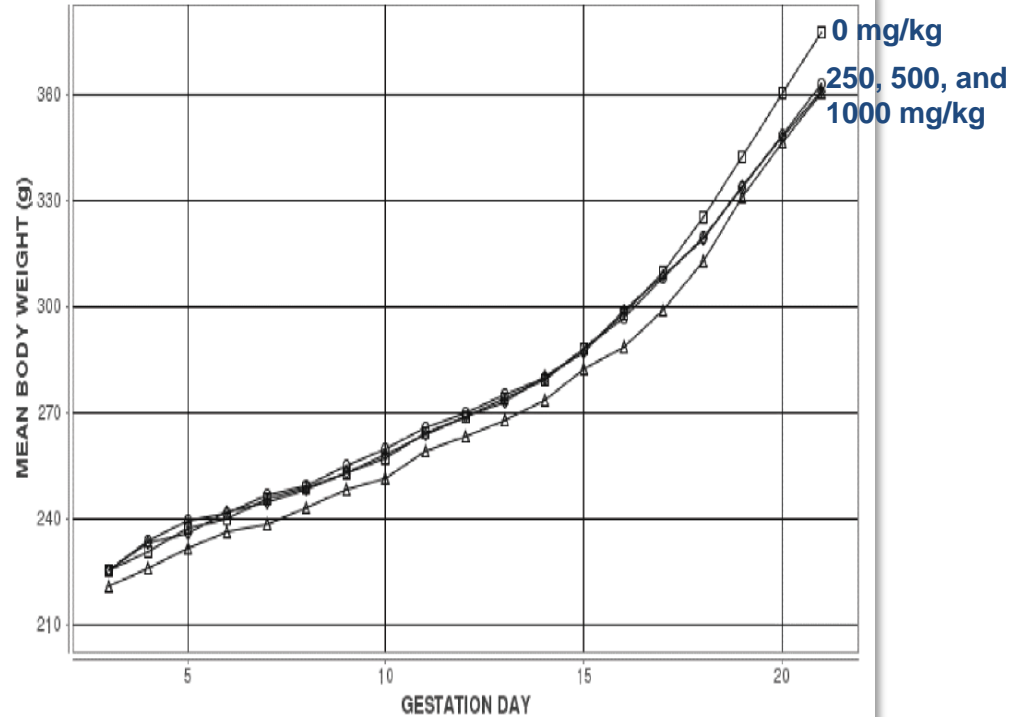


- **Doses: 0, 250, 500, or 1000 mg/kg/day (gavage)**
- N=10 time-mated, female rats per group
- Maternal endpoints: Clinical observations, body weights, feed consumption, and uterine parameters
- Fetal endpoints: Fetal weight, external examination, and litter parameters including number of live/dead fetuses, and sex ratio



Dose Range-Finding Study: Maternal Findings

- No dams were removed from study due to morbidity or mortality
- No notable clinical signs of toxicity were noted in any dose group
- No treatment-related effects on maternal body weight





Dose Range-Finding Study: Uterine and Litter Parameters

Endpoint	0 mg/kg	250 mg/kg	500 mg/kg	1000 mg/kg
Maternal Terminal Body Weight (g)	363.1 ± 12.0	360.8 ± 12.9	377.8 ± 7.3	361.3 ± 16.0
Gravid Uterine Weight (g)	80.57 ± 10.8	84.13 ± 14.1	94.56 ± 4.7	93.54 ± 5.5
No Litters	10	10	10	10
No. Live Fetuses	97	82	128	108
No. Live Fetuses per Litter	10.8 ± 1.6	11.7 ± 1.9	12.8 ± 0.7	13.5 ± 0.6
No. Resorptions (Early + Late)	5	1	3	4
No. Whole Litter Resorptions	0	0	0	0
Post-implantation Loss	10.2 ± 7.4 %	0.9 ± 0.9%	2.3 ± 1.2%	3.4 ± 1.3%
Fetal Weight per Litter (g)	5.39 ± 0.05	5.39 ± 0.17	5.40 ± 0.05	5.08 ± 0.40
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Values are reported as counts or mean ± standard error; (g) = grams

- No treatment-related findings associated with number of fetuses, resorptions, or post-implantation loss
- Small decrease in fetal weight at 1000 mg/kg



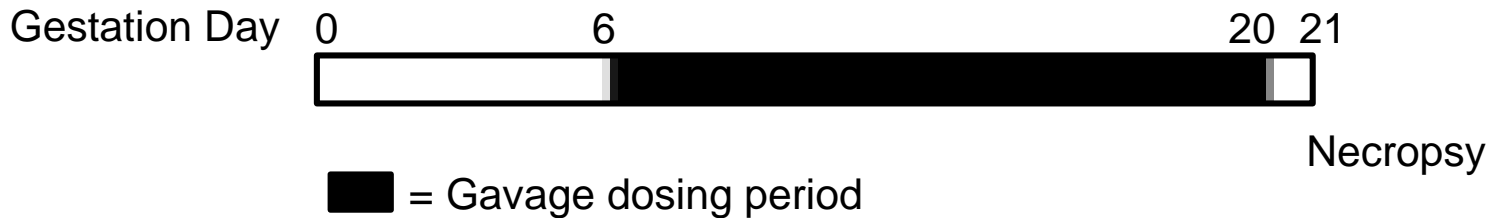
Dose Range-Finding Summary

- No maternal toxicity noted up to 1000 mg/kg/day
- No significant fetal toxicity noted up to 1000 mg/kg/day

- Based on these findings, doses of **0, 250, 500, and 1000 mg/kg/day** were selected for the main study.



Main Study Design

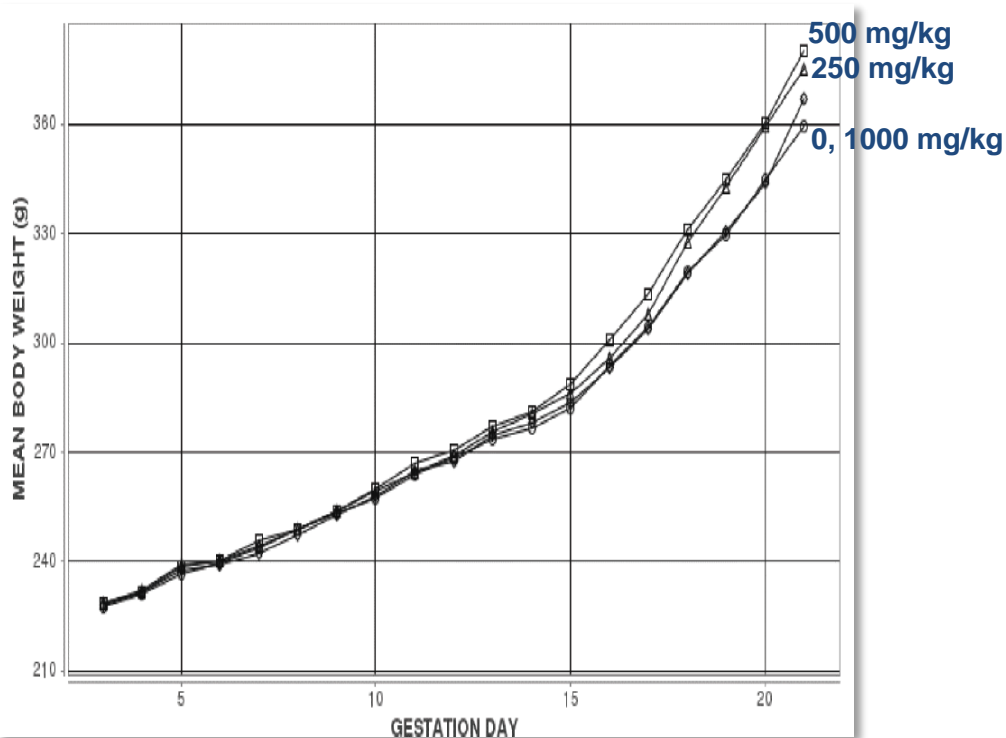


- **Doses: 0, 250, 500, or 1000 mg/kg/day (gavage)**
- N=25 time-mated, female rats per group
- Additional endpoints (in addition to those assessed in the Dose Range-Finding Study):
 - Fetal: Visceral, head, and skeletal examinations



Main Study: Maternal Findings

- One dam was euthanized on GD21 (hypoactivity, dehydration, cold)
 - Unclear if related to DMAE
- Clinical observations were limited to single or sporadic incidences
 - Vaginal discharge in all groups, no dose-relationship
- No dose-related effects on maternal body weight gain





Main Study: Uterine and Litter Parameters

Endpoint	0 mg/kg	250 mg/kg	500 mg/kg	1000 mg/kg
Maternal Terminal Body Weight (g)	359.6 ± 8.8	375.2 ± 5.3	380.3 ± 5.1	361.4 ± 8.5
Gravid Uterine Weight (g)	80.18 ± 7.4	95.85 ± 3.9	96.17 ± 3.8	85.25 ± 6.4
No. Litters	19	20	20	24
No. Live Fetuses	209	265	260	249
No. Live Fetuses per Litter	11.00 ± 1.12	13.25 ± 0.60	13.00 ± 0.56	11.32 ± 1.07
No. Resorptions (Early + Late)	9	10	10	14
No Dead Fetuses	0	0	0	11
No. Whole Litter Resorptions	0	0	0	0
Post-implantation Loss	5.05 ± 1.6%	3.80 ± 1.5%	3.45 ± 1.1%	11.17 ± 5.6%
Fetal Weight per Litter (g)	5.38 ± 0.15	5.26 ± 0.05	5.33 ± 0.06	5.40 ± 0.09

Values are reported as count or as mean ± standard error; (g) = grams

- No treatment-related findings associated with number of fetuses, resorptions, post-implantation loss, or fetal body weight



Main Study: Fetal Findings

- External Findings:
 - Single or sporadic incidences/findings

- Visceral Findings:
 - Single or sporadic incidences/findings

- Head Findings:
 - No exposure-related findings



Main Study: Fetal Skeletal Findings

Endpoint		0 mg/kg	250 mg/kg	500 mg/kg	1000 mg/kg	Historical Controls
No. fetuses examined		296	283	279	247	1,324
No. litters examined		23	21	21	19	104
Short Thoracolumbar SNR, (Variation)	Fetuses	56 (26.8%)**##	56 (21.2%)	59 (22.7%)	100 (38.5%)**#	9.9 - 26.8%
	Litters	17 (89.5%)	18 (90%)	18 (90%)	19 (86.4%)	66.7 – 91.3%
Supernumerary sites, skull (Variation)	Fetuses	1 (1%) **##	3 (2.3%)	2 (1.6%)	13 (10.2%) **#	0.7 – 2.9%
	Litters	1 (5.6%) **	3 (15%)	2 (10%)	10 (50%) **	4.3 – 11.11%

(SNR) = supernumerary ribs

Statistically significant ($P \leq 0.05$) according to mixed effects logistic regression. ## $P < 0.01$.

* Statistically significant ($P \leq 0.05$) according to Cochran-Armitage (trend) or Fisher exact (pairwise) test. ** $P < 0.01$

- Increased incidence of short thoracolumbar ribs & supernumerary sites in the skull
- No treatment-related malformations



- DMAE was well tolerated and there were no treatment-related effects on mortality, body weights, or feed consumption
- Clinical observations were limited sporadic incidences or had a lack of dose-response
- No effects on uterine or litter parameters, including implantations, litter size, live fetuses per litter or fetal weight
- Fetal findings
 - Limited to common background findings and singular or sporadic incidences
 - Skeletal variations
 - Increased incidence of short thoracolumbar ribs (a variation) at 1,000 mg/kg
 - Increased incidence in the number of supernumerary sites, or ossification sites, in the skull in 1,000 mg/kg



Under the conditions of this prenatal study:

- ***Equivocal evidence*** of developmental toxicity of DMAE in Hsd:Sprague Dawley SD rats based on increased incidences of:
 - Short thoracolumbar ribs
 - Supernumerary sites in the skull
- These findings occurred in the absence of overt maternal toxicity



Questions?